Multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopment among preterm neonates

---

SYNOPSIS SUBMITTED

To

Maharishi Markandeshwar (Deemed to be University)

Mullana, Haryana, India

In partial fulfillment of the requirements for the degree

Doctor of Philosophy

(Physiotherapy)

SUBMITTED

By

Neha Sharma

Roll No: 1820742

Multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopment among preterm neonates

---

SYNOPSIS SUBMITTED

To

Maharishi Markandeshwar (Deemed to be University)

Mullana, Haryana, India

In partial fulfillment of the requirements for the degree

Doctor of Philosophy

(Physiotherapy)

SUBMITTED

By

Neha Sharma

Roll No: 1820742

20.09.2021

PRINCIPAL

MM Institute of Physiotherapy & Rehabilitation

Maharishi Markandeshwar Deemed to be University

Mullana-Ambala-133203

MAHARISHI MARKANDESHWAR INSTITUTE OF PHYSIOTHERAPY AND REHABILITATION

MAHARISHI MARKANDESHWAR (DEEMED TO BE UNIVERSITY)

(Accredited by NAAC with Grade "A")

MULLANA-AMBALA, HARYANA

Certificate

This is to certify that the PhD thesis synopsis / protocol on, **"Multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopment among preterm neonates"** has been done by Neha Sharma, 1820742, under my supervision. I am satisfied with the work presented by the candidate towards the partial fulfillment of Doctor of Philosophy (PhD) in Physiotherapy. This is an original work submitted only to Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana, and is free of any plagiarism at the time of her submission.

20/09/2021

Supervisor

Dr. Asir John Samuel, PhD (Physiotherapy),
Associate Professor,
MMIPR, MM (DU),
Mullana-Ambala, Haryana.

Dr. Asir John Samuel,
PhD (Physiotherapy),
MPT (Neuro & Pediatric Neuro),
BPT, MIAP (L-27452), BSc, DYScEd
Assoc. Prof, MMIPR, MM (DU)

20.09.2021

PRINCIPAL

Date: 20-09-2021

List of Abbreviations

BW: Birth weight

GA: Gestational age

CGA: Corrected gestational age

NIPS: Neonatal infant pain scale

PIPP-R: Preterm infant pain scale- revised

N-PASS: Neonatal pain agitation sedation scale

NFCS: Neonatal facial coding system

INFANIB: Infant neurological international battery

CRIES: Crying requires increased oxygen administration increased vital signs expression sleeplessness

TIMP: Test of infant motor performance

NAPI: Neurobehavioral assessment of preterm infant

NNNS: NICU Network Neurobehavioral scale

FT: Facilitated tucking

KMC: Kangaroo mother care

NNS: Non-nutritive sucking

List of Tables

Sr. No.	Title	Page no.
2.1.	Pain pathway development	12
2.2.	Common scales used for measuring neonatal pain	55
2.3.	Studies related to MSS and STT in improving procedural pain and neurobehavioral development	56-58
3.1.	Outcome measures for the study	63-64
3.2.	Intervention details for Experimental Group	71-73

List of figures

Sr. No.	Title	Page no.
1.1.	Most common invasive procedures performed in NICU	2
1.2.	Consequences of neonatal pain	4
1.3.	Non-pharmacological interventions in NICU based on different types	7
2.1.	Common painful procedures performed in neonates during NICU Stay	15
3.1.	Sample size estimation for matched pairs	67
3.2.	Sample size estimation for two groups	68
3.3.	Flowchart of participant inclusion	70
3.4.	Flowchart of allocation, intervention and outcome details	74

Table of content

Sr. No.	Content	Page no.
1.	**Introduction**	1-10
2.	**Review of literature**	11-59
3.	**Methodology**	60-75
4.	**Discussion**	76-78
5.	**References**	79-87
	Annexures	

Abstract

Background: Repeated painful stimuli cause physiological, behavioral and social, and neurodevelopmental problems in neonates admitted in neonatal intensive care units (NICU). The purpose of this study is to determine the effects of multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopmental maturity among neonates admitted in NICU.

Purpose: To determine the combined effects of multisensory stimulation (MSS) and soft tissue therapy (STT) in managing procedural pain and promoting neurodevelopment in neonates undergoing repetitive painful procedures during their Neonatal intensive care unit (NICU) Stay.

Methods: Total 66 preterm neonates admitted in NICU will be recruited for this trial. The intervention will be given for 5 consecutive days to one of the groups. Group A will receive both MSS and STT; Group B will receive only routine NICU care. The Premature infant pain profile-Revised (PIPP-R) and Neonatal pain, agitation and sedation scale (N-PASS) will be used for assessing procedural pain, and some components of Infant Neurological International Battery (INFANIB) and Premie neuro scale will be used for assessing neurodevelopmental maturity. Relevant parametric or non-parametric test will be used to analyze the data for all outcomes.

Discussion: This is a study protocol analyzing the combined effects of non-pharmacological interventions (MSS & STT) in preterm neonates.

Keywords: Neonates; NICU; Procedural; Pain; Soft tissue therapy

1. Introduction

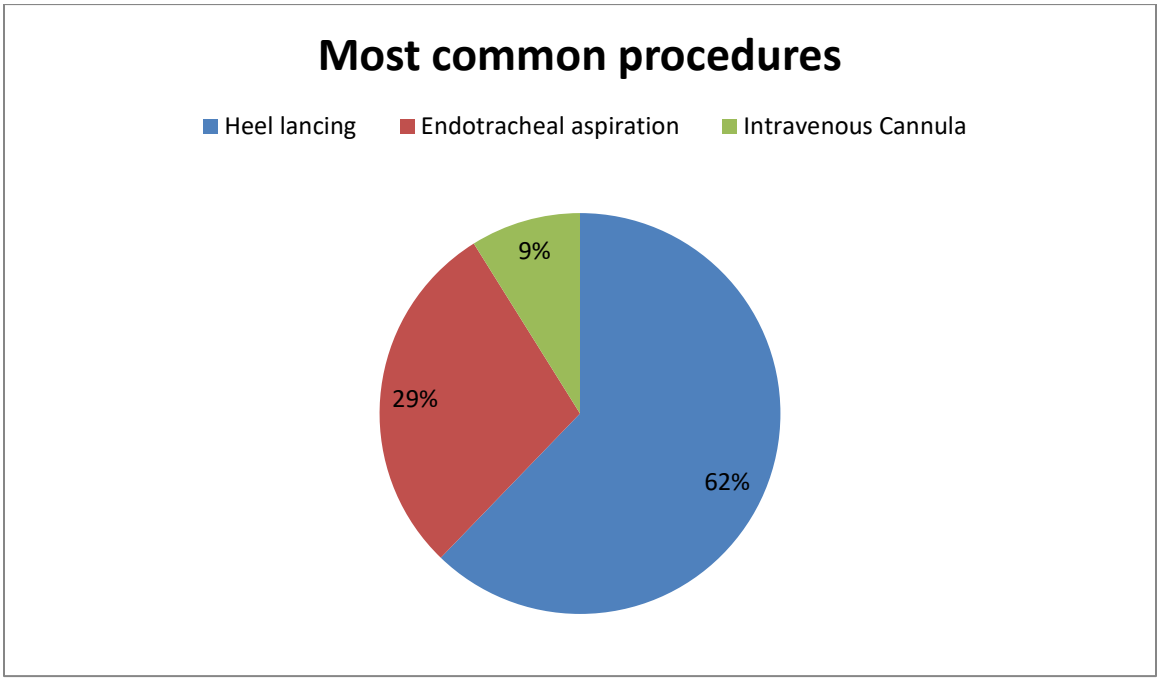
Neonates alive before 37 weeks of gestation are termed as preterm. It has sub categories based on gestational age.[1] Repeated painful procedures are common in neonates who require intensive care.[2] Pain in neonates is difficult to assess due to their inability to express their feelings verbally.[3] Neonates admitted in Intensive care unit are exposed to significant repeated painful procedures at the time when nervous system is developing and sensitive to changes in sensory experience. Neonatal painful procedures varies from 7.5 to 17.3 per week during NICU Stay.[4] in the first 14 days of admission in intensive care unit.[5] Increased activity of spinal and cortical nociceptive pathways in preterm and term neonates causes increase in hyperalgesia progressively.[5] Pain in neonatal period is associated with detrimental effects on future pain response, sensory processing, and neurodevelopmental outcomes. Acute noxious stimuli cause changes in behavioral response and physiological parameters following birth. These responses are also evident in most preterm neonates, although degree, latency and nature may vary.

1.1. Reasons for neonatal pain

One of the most common invasive procedures performed in the NICU is a heel prick or heel prick / needle.[6] This procedure is a needle stick in an infant's heel that is used to take a blood sample to check lab tests, blood sugar, general chemistry, full blood count, and blood tests. Usually, getting the amount of blood needed for the test requires squeezing the heel, which is more painful for the infant than the vein.[6] Another painful procedure that may be necessary for infants with severe respiratory failure is

endotracheal intubation, a procedure performed on both adults and infants that allows access to the airways for respiratory support by mechanical ventilation.[6]

Figure 1.1: Most common invasive procedures performed in NICU[3]



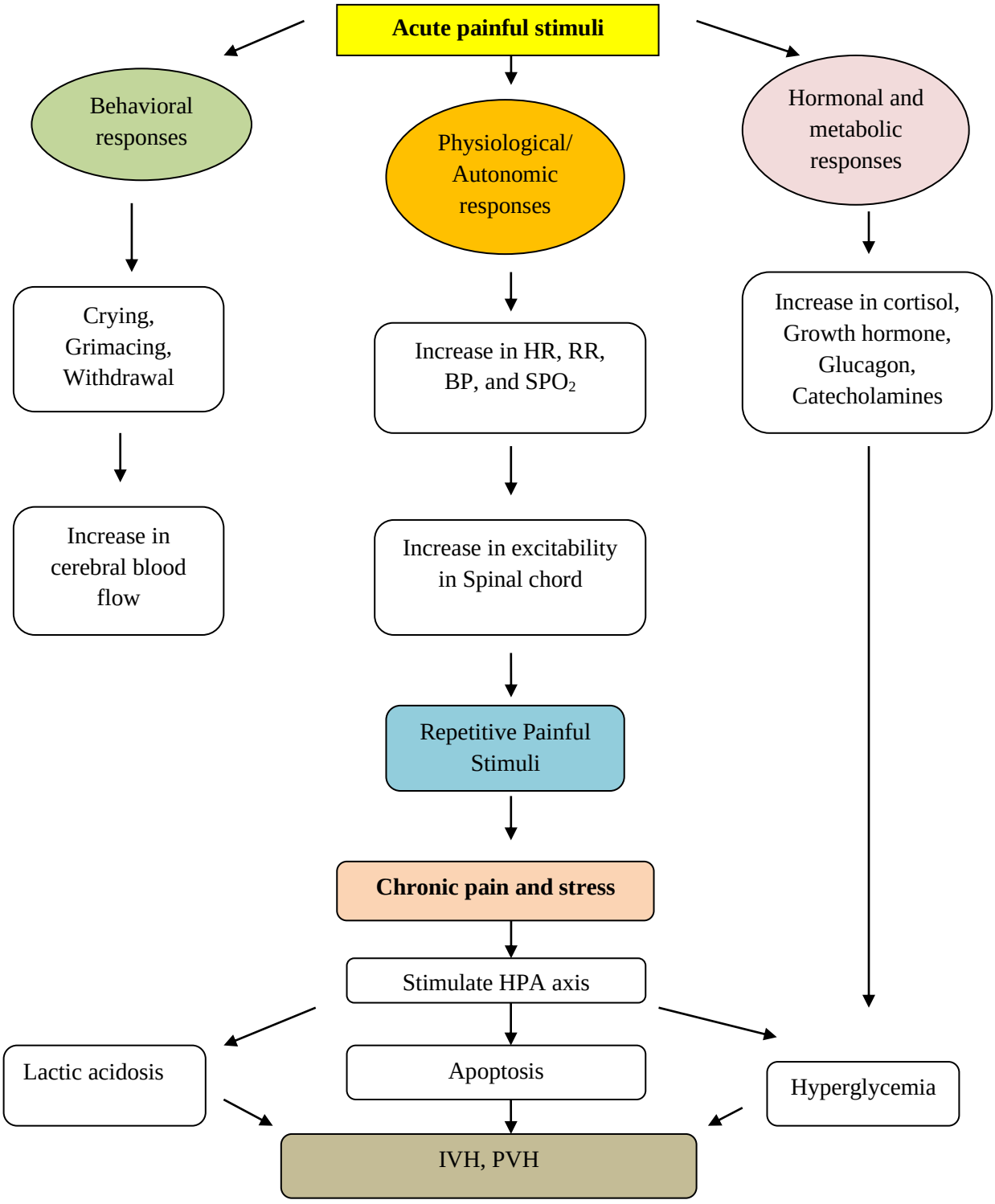
1.2. Neonatal pain and its consequences

Pain causes stress in neonates with adverse multi-system physiologic consequences while admitted in NICU.[6] It causes activation of sympathetic nervous system triggered by fight or flight response, and finally leads to the release of glucocorticoids. Physiological parameters, such as heart rate, blood pressure, and heart rate variability are increased with pain. It leads to rise in venous and intracranial pressure, whereas decrease in arterial oxygen saturation and blood flow towards the skin.[6,7] Repeated painful procedures in hospitalized neonate's causes increase in intra-cranial pressure and leads to intra- ventricular hemorrhage (IVH) and periventricular leukomalacia

(PVL).[8] Untreated pain causes long-term consequences. The long- term consequences of untreated pain have negative impact on neonatal brain. These negative impacts mainly associated with sensorimotor and cognitive development, pain responses, and behavior (mood problems). [1,9] Early painful experiences shape the somatosensory areas of perceptual, cognitive, and social development.[1,9] Sensorimotor impairment most commonly in children are cerebral palsy, delayed development, impaired vision, impaired hearing deafness, and delayed developmental trajectory. Early painful procedures affect neonatal brain growth, which is directly related to the cognition.[10]

These long-term consequences may persist into adolescence and young adulthood. Preterm boys are at greater risk for having poor neurodevelopment outcomes as compared to preterm girls because girls are more vulnerable to brain development with slower growth of basal ganglia, thalamus, and total brain volumes, when experiencing early pain.[10] The following long-term consequences are: learning disorders, cognitive deficits, motor deficits, behavioral problems, attention deficits, and poor adaptive behavior. The smallest and sickest neonate is at the highest risk for abnormal neurodevelopment.[9,10]

Figure 1.2: Consequences of neonatal pain[11]



Abbreviations: HPA: Hypothalamic pituitary axis, IVH: Interventricular heamorrhage, PVH: Periventricular Leukomalacia

1.3. Neonatal pain management

Effective pain management techniques are suitable standard of care for newborns undergoing repetitive painful procedures, and may potentially improve their neurodevelopmental and clinical outcomes.[12] Pharmacological, Non-pharmacological, or behavioral approaches can be used to manage neonatal pain in NICU settings. Non-pharmacological management approaches include non-nutritive sucking, Oral glucose and sucrose, Breastfeeding, therapeutic massage, facilitated tucking, kangaroo mother care, Music therapy, Acupuncture, and Multisensory stimulation (MSS). Most of the above non-pharmacological approaches prevent the pain sensation from travelling to Central nervous system (CNS) by activating a “gate control mechanism”. Pharmacological approaches include local and topical anesthetics which reduce the actual pain caused routine investigatory procedures.

1.4. Pharmacological interventions

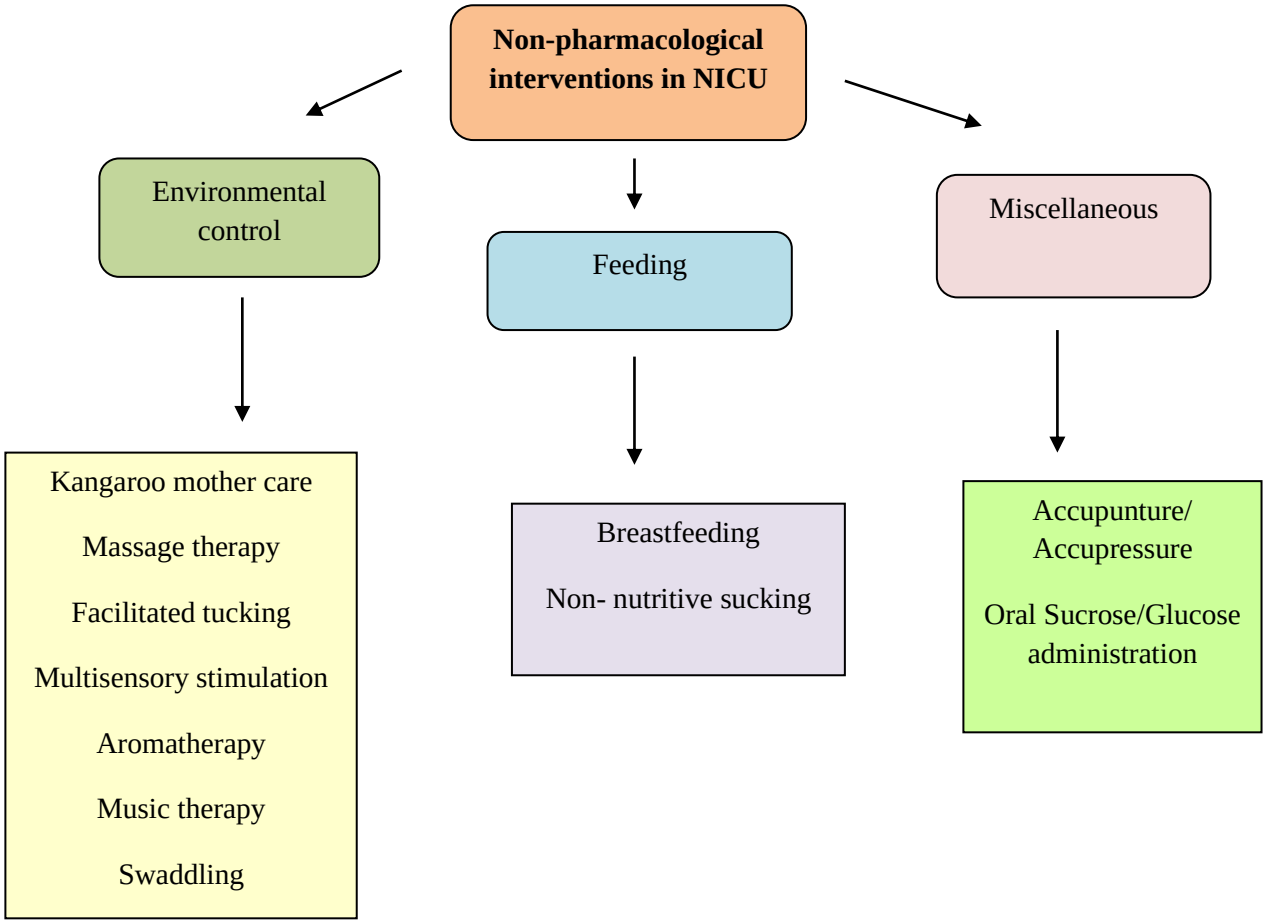
Opoids such as Morphine and Fentanyl are the mainstay of neonatal chronic or severe pain.[13] A Non-opoids drug such as Acetaminophen, Ibuprofen, and Naproxene are mostly commonly used in ventilated neonates. Opioids provide both sedation and analgesia, have a wide therapeutic window, and reduce responses to hemodynamic and metabolic stress, but they do not induce amnesia. Benzodiazepines are a better choice when dementia devices are needed.[13] Morphine and fentanyl are the most commonly used opioids in the NICU population. Morphine is the most commonly used opiate for pain relief, but there is wide variation in dosage and clinical use. Morphine has a ceiling effect; After reaching a certain therapeutic level, higher doses produce more side effects than increase pain relief. Clinical experience shows that a ceiling

effect can be achieved when doses up to 0.5 mg/kg are used. Morphine has a slow analgesic effect due to its low lipid solubility, especially in premature infants. Another commonly used opioid, fentanyl has a rapid onset of action (2-3 minutes), a short duration of action (60 minutes with a bolus), and minimal hemodynamic effects. Prolonged elimination occurs with infusion of fentanyl, leading to a rebound in plasma concentrations. Chest wall stiffness may occur with rapid intravenous administration of fentanyl.[13]

1.5. Non- Pharmacological interventions

Non- Pharmacological interventions are adjuvant to pharmacological interventions. These interventions utilize behavioral and environmental approaches by activating “gate control mechanism’’, which prevents pain sensation from traveling to CNS.[14] Non-pharmacological approaches individually or in combination with any other non-pharmacological approach are in trend now a day in reducing procedural pain as well as promoting neurodevelopment among term and preterm undergoing repetitive painful procedures.[15] Non-pharmacological management of neonatal pain primarily involves the prevention of stressful pain-related experiences in the vulnerable group of premature and full-term infants. During hospitalization in the NICU, premature infants undergo an average of 7 to 17 painful procedures per day and experience other extreme or moderate stress events, such as intubation, eye examination, puncture lumbar puncture, heel prick, and nasogastric tube placement.[16] The scientific, evidence-based, non-pharmacological management of acute pain in infants includes the following: (i) breastfeeding or breast milk, (ii) non-nutritive sucking, (iii) Facilitated tucking, (IV) Swaddling, (v) Acupuncture, and (vi) Music therapy.

Figure 1.3: Non-Pharmacological interventions in NICU based on different types[14]



1.5.1. Environmental Control

No n-pharmacological interventions such as Kangaroo mother care, Aromatherapy, Music therapy, Swaddling, facilitated tucking, and MSS creates comforting environment for the neonate which produces pain relieving effects. Environmental comfort through non-pharmacological interventions causes release of neuropeptide, Cholecystokinin, which is associated with pain relieving effects.[14] These interventions simulate the environment of maternal womb, which helps in providing analgesics effects. Music therapy involves neonatal attention, and provide maternal womb environment, which distracts them from pain and decreases pain sensation.[14]

1.5.2. Feeding methods

Feeding methods involves breastfeeding and Nonnutritive sucking which produces analgesic effects through the release of neuropeptide, cholecystokinin. Due to familiar maternal odor, breastfeeding leads to release of cholecystokinin.[14] Non-nutritive sucking causes release of cholecystokinin which interacts with opioids and produces pain relieving effects through activation of oral sensory nerve.[14]

1.5.3. Miscellaneous

Oral glucose and sucrose is mostly used as non-pharmacological interventions in NICU. Glucose/Sucrose may produce its analgesic effects via endogenous opioid pathways, or also through increase in dopamine and acetylcholine.[14] Acupuncture and acupressure involve spinal pain pathways, which leads to attenuation of pain signaling, if acupuncture is performed with needle. Mechanism of pain relief through these interventions is still unknown.[14]

1.6. Multisensory stimulation

MSS is closely related to the principles of sensory stimulation therapy, which is characterized by developmental sensory inputs consisting tactile, auditory, oral, visual, kinesthetic, vestibular, and olfactive, to encourage and preserve the development of existing abilities, and also to avoid the detrimental effects of the environment.[17,18] MSS shows improvement in neurodevelopment, weight gain, and reduction in stress levels.[17,18] MSS moreover encourage the process of neuroplasticity along with the

maturation of the brain electrical activity.[17] MSS helps in releasing oxytocin, which is anti-stress hormone, and further helps in decreasing neonatal procedural pain.

1.7. Soft tissue therapy

The main mechanism behind STT is that it stimulates vagal activity, which helps in decreasing pain, and improving weight gain.[19] Another mechanism of pain reduction by STT is obtained through the gate theory of pain control where STT stimulates large-diameter nerve fibers that may inhibit inputs from small-diameter nerve fibers. Soft tissue therapy (STT) is acknowledged as a potential therapeutic intervention for managing procedural pain among neonates.[14] Therapeutic massage or STT is considered as an earliest form of treatment in medical history. STT is defined as systematic touch by human hands which stimulate neonate's tactile sensation. It is also defined as manipulation of soft tissues and muscles in the body to enhance health and well-being.[14] Tactile/touch sensation is the first and fastest developing sense in neonates after birth, and most important for growth and development in preterm neonates, who are deprived of gentle human touch. It has remedial effects on both preterm and term neonates.[14]

As recommended by American Academy of Pediatrics, combination of several non-pharmacological approaches reduces pain effectively in preterm and full-term neonates.[20] In 2006, an policy statement is published by American academy of pediatrics and Canadian pediatric society that each healthcare facility should have neonatal pain control program.[20] Combined non-pharmacological therapies have synergistic effects. They are more effective when given in combination than single, and

also have proven safe for repeated procedural pain among preterm neonates. MSS decreases pain scores and improves neurobehavioral development, but combined effects of MSS and STT are till now not explored. Hence, there is a definite need of the study.

1.8. Need of the study: To the best of our knowledge, there is no study analyzing the combined effects of MSS and STT in preterm neonates undergoing painful procedures.

1.9. Research question: Is MSS and STT will effective in reducing pain and improving neurodevelopment among preterm neonates?

1.10. Objectives of the study: To identify the impact of 5 days MSS and STT interventions on pain scales (PIPP-R & N-PASS), and neurobehavioral outcomes (INFANIB & Premie-Neuro) among preterm neonates

1.11. Research hypothesis

1.11.1. Null hypothesis: There will be no significant difference between Group A (MSS+ STT) and Group B (Routine NICU care) in procedural pain and neurodevelopment after 5 days of intervention.

1.11.2. Alternate hypothesis: There will be no significant difference between Group A (MSS+ STT) and Group B (Routine NICU care) in procedural pain and neurodevelopment after 5 days of intervention.

1.12. Aim of the study: To determine the effects of MSS and SFT in relieving procedural pain and improving neurobehavioral outcomes.

2. Review of literature

Pain is a perception, not sensation, and is defined as an unpleasant sensory experiences associated with tissue damage given by the International association for the study of pain (IASP), updated in 1994 and 2002.[20] Neonatal pain framework (acute, persistent, prolonged pain) was derived from scientific literature on neonatal pain assessment and evaluation, neurophysiological and clinical aspects of neonatal pain.[20] This initial framework of neonatal pain incorporates with the neonatal pain experiences, behavioral, and physiological responses of neonates. Pain is a subjective phenomenon which requires higher and emotional cortical functions not apparent in the newborns.[21] The assessment of pain in the newborn mainly focuses on acute pain, while persistent, persistent or chronic pain is relatively neglected.[22] The acute pain occurs immediately with the onset of tissue damage or irritation of the inflamed area, and it usually persists during the irritation or for a short time afterward (some infants have slower pain relief than other children).[22] Descending inhibitory fibers develop from brainstem nuclei on the spinal cord, reaching only the cervical part of the spinal cord after 30-32 weeks; they have not reached the lumbar spine after 30 weeks, allowing increased sensitivity to pain in the lower limbs.[23]

2.1. World health Organisation (WHO) classification for preterm neonate

WHO sub-categorizes preterm neonates based on their gestational age. Preterm neonates < 28 weeks of gestation are extremely preterm, neonates between 28-32 weeks of gestation are very preterm, and between 32-37 weeks are moderate to late preterm.

Table 2.1: Pain pathway development

Time Period	Sensory nerve endings development
6th week of gestation	Synaptic development between sensory fibers and interneuron's in dorsal horn
7th week of gestation	Perioral region
11th week of gestation	Face, palms, and soles
12th week of gestation	Neural pathway connection between nociceptive nerve endings peripherally with spinal dorsal column
15th week of gestation	Proximal extremities and trunk
20th week of gestation	Cutaneous areas and mucus membranes Nociceptive pain signaling
24th to 26th weeks of gestation	Neural pathway connection between spinal dorsal horn cells to thalamic tract
30th week of gestation	Myelination of the neurons of brainstem and thalamic tract

2.2. Pain perception and its elements

Pain perception causes chemical changes inside the tissues which are are harmful. Cognition plays important role in the recognition of pain perception.[21] Elements which respond to the emotional, cognitive, and physiological aspects of pain are emotional consequences and behavioral responses. Nociception is the physiological mechanism

involved in the pain phenomenon.[10] The ability of nerve to detect painful stimuli, and transmit this information to the brain is termed as nociception. It provides proper description of a neonate's response to a painful tissue damaging stimuli.[10]

A pain response enables a neonate to function in a challenging, dynamic, and potentially risky environment, and also plays an integral part of an adaptive biological system of neonates.[10] Pain response represents pain modulation, emotional and behavioral responses, and integration by the peripheral nervous system, spinal cord, and brain. All of these concurrent responses are important elements of neonatal pain perception and stress.[10]

2.3. Common painful procedures performed in neonates during NICU stay

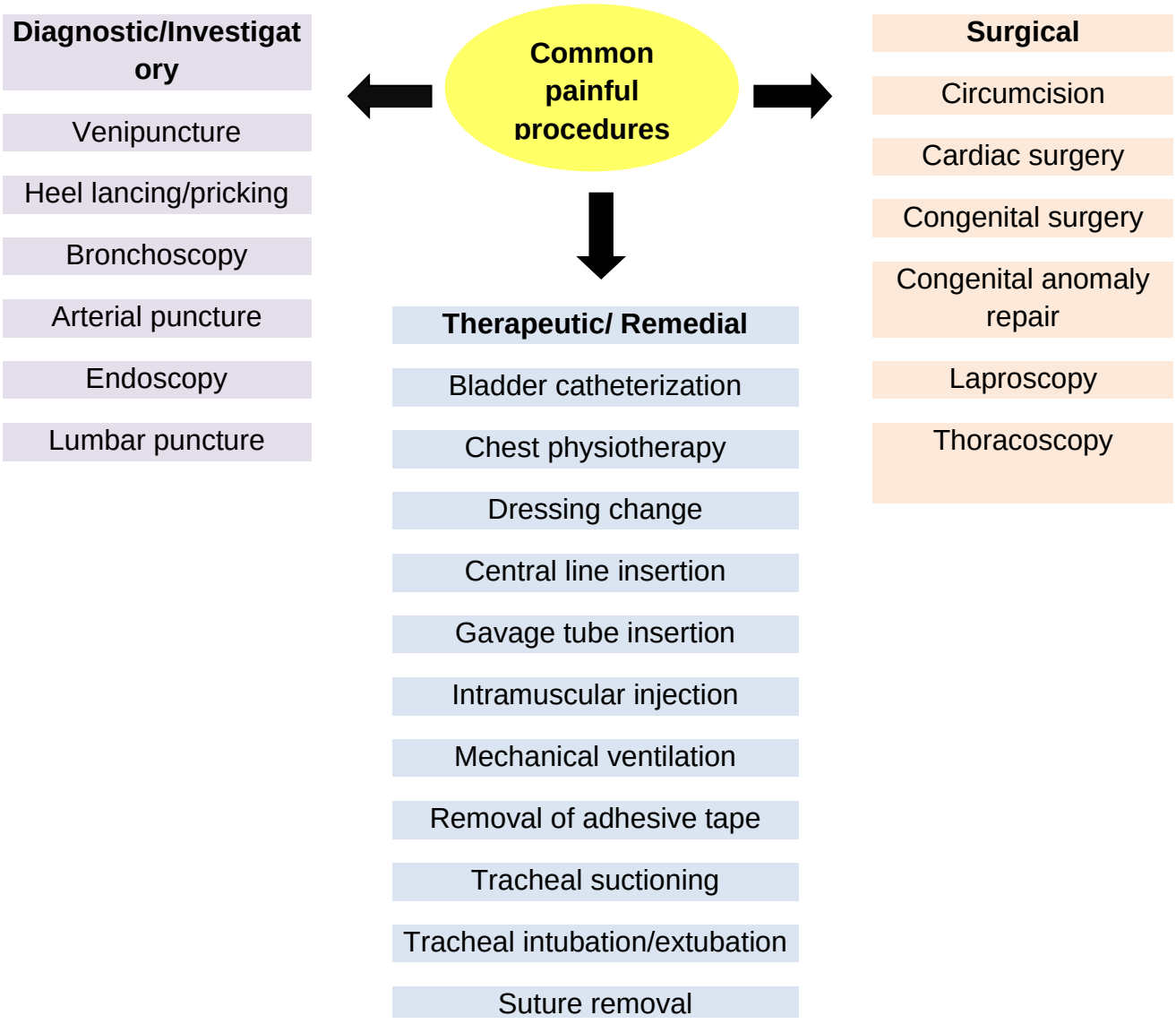
In NICU, Over 3000 procedures have been recorded, 74% in neonates under 31 weeks gestation underwent repeated painful procedures. Heel blood sampling was the most common procedure (56%), followed by endotracheal aspiration (26%) and intravenous cannula (8%). Invasive procedures that can cause pain or discomfort to babies are often performed on infants who are admitted to the neonatal intensive care unit. Reducing the number of procedures, modifying them, or providing enough pain relievers can alleviate some of the symptoms of pain and discomfort.

Preterm neonates are most frequently subjected to painful procedures during their NICU stay, and receive highest numbers of painful events. Procedural pain is associated with investigation, treatment and diagnostic procedures performed in neonates during their NICU stay.[1] Untreated procedural pain leads to short and long term adverse squealae. These sequelae include altered brain development, physiologic instability, and abnormal

neurodevelopment. Studies have demonstrated elevation in stress related markers, even with the simple routine procedures such as heel lancing or adhesive tape removal.[1]

The most frequently described painful procedures include heel lancing/heel stick/ heel prick, Arterial puncture, Venipuncture, Percutaneous Central venous catheter insertion, Intramuscular/subcutaneous injection, lumbar puncture, immunizations, laceration suture during changes, removal of adhesive tapes and Intravenous cannulation. Repeated painful stimuli can trigger behavioral changes in a neonate.[6]

Figure 2.1: Common painful procedures performed in neonates during NICU Stay



2.4. Cortisol as a stress hormone

Newborns with greater cumulative exposure to procedural pain were associated with lower cortisol responses to stress at 32 postmenstrual weeks, independent of at gestational age and baseline disease severity. Unlike infants born at 28 weeks of gestation, at adjusted ages of 8 and 18 months, cortisol levels were elevated, and this level was associated with the frequency of laceration procedures from birth to age equivalent. Procedure pain continuously induces both stimulatory and inflammatory reactive oxygen species and can suppress the growth of premyelinated cells.

2.5. Neonatal Pain management strategies

Effective pain management techniques are suitable standard of care for newborns undergoing repetitive painful procedures, and may potentially improve their neurodevelopmental and clinical outcomes.[12] Pharmacological, Non-pharmacological, or behavioral approaches can be used to manage neonatal pain in NICU settings. Pharmacological strategies adopted in NICU consider the use of drugs to treat and relieve pain. Non-pharmacological strategies are biased towards other methods of care, especially in the adaptation phase of the pain experience.

2.6. Pharmacological neonatal pain management strategies

Pharmacological approaches include local and topical anesthetics which reduce the actual pain caused by skin-breaking procedures. These procedures can be used for managing transient, mild or acute pain.[15] Opoids such as Morphine or Fentanyl are the mainstay of chronic or severe pain. A Non-opoids drug includes sedatives and anesthetic agents such as Ibuprofen and Acetaminophen are mostly used in ventilated

neonates. Non-pharmacological approaches individually or in combination with any other non-pharmacological approach are in trend now a day in reducing procedural pain as well as promoting neurodevelopment among neonates undergoing repetitive painful procedures.[15]

Clinical observations of new treatment modalities, including synthetic, non-opioid opioids, and local techniques have been introduced in the Neonatal Intensive Care Unit (NICU).[24] Importantly, new concepts of the link between pain exposure, analgesics, and neuro-digestion have emerged.

2.6.1. Topical anesthetics as analgesics

By blocking Na + channels, Lidocaine inhibits axonal conduction. Lidocaine infiltration is commonly used for various penile masses for circumcision. In this case, its use was found to be effective in reducing the pain response to vaccination for 4 months after circumcision compared to neonates given as a placebo. Compared to a dorsal penile block or a mixture of topical anesthetic cream Eutectic mixture of local anesthetic cream (EMLA), the ring patch has been shown to be the most effective method of relieving pain during circumcision.

Local anesthetics are effective for certain types of intervention pain such as vasospasm, lumbar puncture or venocentesis. Tetracaine and EMLA are also used topically, with varying degrees of success in managing neonatal pain.

2.6.2. Opioid Therapy in managing neonatal pain

Opioids are the most effective treatment for moderate to severe pain in patients of all ages. They produce both analgesic and sedative effects, have a wide therapeutic window and also reduce the physiological stress response of the infant. Morphine and

fentanyl are the most commonly used opiates, although some are injected into the NICU settings.

2.6.3. Morphine as an analgesic

Morphine is the opioid most commonly used for neonatal analgesia, often administered as a continuous infusion in mechanically ventilated or postoperative infants, or intermittently for the relief of acute pain associated with invasive procedures. Its efficacy and safety for these indications have not been established, but are still under active investigation.[25]

Morphine improves duration of mechanical ventilation in ventilated neonates. Morphine analgesia is associated with significant adverse events in premature infants, but may or may not alter their long-term cognitive or behavioral outcomes. To verify this, 52 full-term infants with postpartum hypoxia due to asphyxia showed less brain damage with magnetic resonance imaging (MRI) and improved neurodevelopmental outcomes in infants given morphine for one week. Early postpartum compared with infants not treated with opioid.[25]

Morphine analgesia may not be associated with the same risk in mechanically ventilated term infants, but may still result in increased duration of mechanical ventilation. To verify this, 62 ventilated term neonates found that postoperative morphine infusion prolonged the duration of mechanical ventilation, but was not associated with apnea, hypotension, or other complications.[25]

2.6.4. Fentanyl as an analgesic

As a highly lipophilic drug, fentanyl provides rapid pain relief with minimal hemodynamic effects in term and preterm infants, although its widespread use is not supported by

evidence from large multicenter RCTs. Fentanyl or its abbreviated derivatives are commonly used for preoperative pain relief in preterm and term infants. To determine this, 20 preterm infants showed a significantly improved overall intubation status in those receiving booster injections of fentanyl compared to morphine. However, no complications occurred after the morphine injection or the booster.[25]

A multicenter RCT involving 131 mechanically ventilated premature neonates (23-32 weeks gestation), fentanyl infusion reduced the acute pain score (PIPP); No difference occurred in persistent pain scores Echelle de Douleur et d' Inconfort du Nouveau-ne) Scale (EDIN) between the two groups, although fewer infants had an EDIN score> 6 for fentanyl (6.8%) compared to placebo group (10.6%). Those who received fentanyl had longer mechanical ventilation and delayed bowel movements.[25] The analgesic Fentanyl is associated with less sedation or hypotension, reduced effects on gastrointestinal motility or urinary retention, but greater tolerance and greater opoids withdrawal than with morphine. A single-center RCT compared infusion of fentanyl (1.5 mcg / kg / h) with morphine (20 mcg / kg / h) in 163 mechanically ventilated neonates and reported that pain scores, response to catecholamine's and birthmarks were similar in both groups. There were no adverse respiratory effects or difficulty weaning from ventilation in the two groups, but decreased beta-endorphin levels and gastrointestinal dysfunction occurred in the fentanyl group.

New practices lead to new diagnoses and complications. Opoids exposure may lead to tolerability, neonatal withdrawal syndrome, or hyperkalemia. Likewise, drug toxicity (eg, paracetamol, propofol) and regional anesthesia can lead to specific complications. Caregivers should familiarize themselves with these issues.[25]

2.7. Non-Pharmacological interventions as pain management strategies

Non-pharmacological interventions have the potential to relieve pain in premature infants and term infants. However, many pain relievers have the opposite effect. Therefore, it is necessary to supplement with pharmacological analgesics. Non-pharmacological management approaches include non-nutritive sucking, Oral glucose and sucrose, Breastfeeding, therapeutic massage, facilitated tucking, kangaroo mother care, Music therapy, Acupuncture, and Multisensory stimulation (MSS).[15]

2.7.1. Kangaroo mother care

Kangaroo mother care (KMC) has beneficial effects in reducing pain and stress among preterm neonates undergoing painful procedures.[26] To verify this, 50 preterm neonates less than 2500g, between 32 – 36 weeks 6 days of gestation undergoing for heel lancing were participated in the study. Preterm neonates randomly allocated into control and experimental group. In experimental group neonates received KMC for 15 minutes prior to, during, and after the procedure, while neonates in control group received blanket swaddling in prone position just 15 min. prior to the procedure. Pain and physiological parameters (Heart rate, oxygen saturation, brow bulge, behavior, nasolabial furrow) were assessed as the outcome measures, and received at the baseline and immediately after the intervention. For measuring pain, PIPP scale was used as an outcome measure, and was scored on the recorded vedio.[26] The procedure was repeated on the same neonate on the duration of 24 hrs to 7 days of gap. The inter-observer agreement for each component of PIPP was also measured through weighted Kappa. It shows excellent inter-rater agreement for each component (average weighted Kappa= 0.84).[26] Preterm neonates in experimental groups shows decrease in

mean score of PIPP (5.38) as compared to the preterm neonates in control group (10.23). Highly statistical significant differences ($p<0.0001$) were noted in the experimental group as compared to control group.[26]

KMC is a simple and inexpensive pain reducing analgesic intervention in preterm neonates undergoing heel prick.[27] To determine, this 24 preterm neonates < 37 weeks of gestation were recruited in the study. Neonates were randomized by Zellen technique into two groups A and B. Neonates in Group A received KMC for three hours before heel prick, while neonates in group B received warmer care for three hours before heel prick for first interfeeding interval and then received KMC for the second interfeeding interval.[27] The procedure was applied for one day for this randomized cross-over trial. Physiological parameters (Heart rate, respiratory rate, Oxygen saturation) were recorded manually by the nurses at every 30 seconds. Along with this, behavioral parameters (crying, awake state) were also measured. All the outcomes were recorded 15 minutes prior to procedure, during the procedure, and immediately after the procedure for 5 minutes. The study results showed no significant differences between the groups for demographic parameters. Significant difference was noted in cardiorespiratory and crying parameters. In group A, baseline parameters for HR were 158.2, during heel stick 171.43, and post heel stick were 161.14, while in group B, baseline parameters for HR is 47.2, during 170.8, and after heel stick is 166.3. HR was improved in group A, when compared with group B. For oxygen saturation, baseline parameters in group A are 98.26, during heel stick 96.55, and after heel stick 97.03, while in group B, at baseline 94.62, during 92.55, and after 92.89, so oxygen saturation improves in group A, while compared with group B. For cry length, in group baseline

parameter were no cry was there at the baseline, during heel sick 5.09, and after the heel-stick was 2.03, while in group B, baseline parameters were 2.44, during heel-stick 45.69, and after heel-stick was 4.01. Cry length was decreased in group A when compared with group B.[27]

2.7.2. Facilitated tucking (FT)

Convenient head-holding posture is defined as *Facilitated tucking* or is "a subform of the baby's nesting method, performed in the lateral position, in the supine position, or in the prone position.[28] FT helps in stabilizing neonatal physiological parameters, preserves their energy, and supports motor development. To verify this, 60 neonates with birth weight more than 2500g, and gestational age > 37 weeks were participated in the study. Neonates were divided into FT group and classical holding group.[28] Neonates received hepatitis B vaccination during the study. Vaccination was performed on Vastus lateralis muscle, and physiological parameters were recorded before the vaccination. Neonates in FT group were kept in FT position (lateral) for 1 min. before the procedure. Vedio recording was taken 1 min. before the vaccination, and ended after 1 min, whereas no treatment was given in control group. The physiological parameters (HR, Body temperature, respiratory rate, oxygen saturation) were measured before, during, and after the procedure.[28] Through vedio recording, NIPS was calculated. No statistical significant differences were noted in demographic characteristics (Gestational age, gender, weight, height). Neonates in FT group shows decrease in mean NIPS score (2.83± 1.18) than scores of neonates in control group (6.47± 1.07). The study concludes that 50% of the neonates in FT group had no pain while 93.4% of the neonates in control group had severe pain.[28]

Sucrose given along with or without FT, helps in reducing pain in neonates undergoing heel prick.[29] To verify this, 72 preterm neonates between 24 to 33 weeks of gestation were recruited in this feasibility trial. Neonates were randomized into three groups (24 in each). Neonates in group A received oral sucrose (20 %), while in group B FT was administered, and in Group C, combinations of both the interventions were given.[29] In group A sucrose was administered 2 minutes orally before beginning the procedure. In group B, FT was administered at the beginning, during, and after the procedure. In group C, FT was given at the beginning along with sucrose, 2 minutes prior to the procedure.[29] Outcome measures were collected in three phases: at the baseline, before beginning the procedure, during the painful procedure (heel prick), and at recovery phase, 3 minutes after the procedure. Bernese pain scale for neonates (BPSN) was taken as an outcome measure to assess pain. Scoring was done through Vedio recording at the baseline, during, and after procedure.[29] The BPSN scale consists of total 9 items. It measures both physiological and behavioral parameters on 3-point scale.[29] The study results showed higher significant difference at the baseline and post BPSN scores during heel prick in group A, while compared with group B and C. During recovery phase, no significant differences were noted in group A and B, accept in group C. The study concluded that sucrose with or without FT shows beneficial effects in reducing pain among preterm neonates undergoing heel pricking.[29]

2.7.3. Oral sucrose/ glucose and Non-nutritive sucking

A RCT recruited 90 neonates in the study to examine the efficacy of glucose and sucrose on hepatitis-B vaccination pain.[30] The neonates were randomly divided into three groups (30 in each). Neonates in Group A received 25% of oral sucrose, Group B

received 25% of oral glucose, and no solution was administered to group C. Oral solutions were given to the neonate through syringe before 30 seconds, and 2 minutes after the vaccination.[30] The pain intensity was measured with NIPS. The NIPS measures six behavioral indicators in preterm and term neonates. A total score of NIPS ranges from 0 to 7. The study results showed no significant differences in demographic characteristics (Delivery type, Apgar score, gender, birth weight, height, gestational age, and head circumference) among the groups. Between the group comparisons shows statistically significant differences in mean pain levels in all the three groups ($p<0.05$), NIPS scores were improved in Group A (sucrose) 2.90±4.4 when compared with Group B (glucose) 3.0 ±1.66, and Group C (no intervention) 5.20±1.03. The study results highlighted that sucrose or glucose reduces crying, duration of crying, and procedural pain in neonates during hepatitis-B vaccination.[30]

Non-nutritive sucking (NNS) is safe and beneficial non-pharmacological intervention in relieving procedural pain among term neonates.[31] To determine this, 42 term neonates with 37- 40 weeks of gestational age, and birth weight between 2500-4000 g were recruited in the study. Term neonates were randomized into two groups. Neonates in experimental group received NNS for 120 s before the procedure (heel pricking), during the procedure and 120 s after the procedure.[31] Neonates in control group didn't receive any intervention for pain relief. Pain intensity was assessed with N-PASS (Neonatal pain agitation sedation scale) at 30 s, 60 s, 90 s, and 120 s from the heel prick. N-PASS having five criteria's and each criterion score range from 0 to 2. Total score range between 0 to 10 was calculated to obtain the final score. Along with pain neonatal physiological and behavioral parameters were also recorded through neonatal Oximeter

and Vedio. Pain assessment was done by watching the Vedio. Along with N-PASS, NIPS and NFCS were also scored by two independent researchers by watching recorded Vedios. The study results showed no statistical significant difference in demographic characters (gender, delivery mode, birth weight, gestational age, gestational age at the delivery) of both the groups ($p>0.05$).[31] The mean pain scores was significantly lower ($p<0.05$) in NNS group (at 30s: 4.73±2.78, 60s: 3.64±3.06, 90s: 2.59±3.08, and around 120s: 2.05±2.94) while mean pain scores were significantly higher in control group (at 30s: 7.90±1.52, 60s: 5.55±3.06, 90s: 5.25±3.51, and around 120s: 4.90±3.99). The study results also revealed strong positive correlation between scores of N-PASS and NIPS ($r= 0.643, 0.775, 0.810$, and 0.819), ($p<0.001$) and also between the scores of N-PASS and NFCS ($r= 0,443, 0.733, 0.799$, and 0.781), ($p<0.001$) at different durations of heel prick response (30s, 60s, 90s, 120s).[31]

2.7.4. Music therapy as an analgesic

A RCT recruited 40 preterm neonates < 2500 g, and gestational age between 29-36 weeks to determine the effects of music therapy on pain responses induced by venipuncture in preterm neonates.[32] Preterm neonates were divided into experimental group (20), and control group (20). Venipuncture was selected as a painful procedure for the study. Neonates in experimental group received music 5 min. before painful procedure and continued until 10 min. after procedure. The music was played on MP4-player with two small speakers which were placed on the both sides of neonate's head inside the incubator at a distance of 20 cm. The music used was made a combination of original womb sounds, and the sounds of mother's singing. Womb sounds were recorded through ultrasonic Doppler of a pregnant woman and mixed with the song

sung by the women.[32] Music was played for the 58 min. total, and among of this 15 min. of recording was played to all the neonates in experimental group. The volume chosen for music was 45-60 dB.[32] Physiological, behavioral parameters and Neonatal facial coding system (NFCS) were taken as outcome measures to assess pain. Outcomes were scored through watching recording for 5 min. before playing the music, and also after playing the music for 5 min., during the sampling, and after sampling for 10 min. Each physiological and behavioral parameter was recorded at 15-s interval in between. The study results revealed that there were no significant difference in the demographic characteristics, no. of blood sampling, and blood sampling time among both the groups. Statistical significant difference were found in physiological (heart rate, oxygen saturation), and behavioral parameters (sleep-wake state, facial expressions). There is decrease in mean scores of physiological and behavioral parameters in experimental group. For Physiological parameters (HR at Baseline: 139.75, during 152.30, and after procedure: 160.95), (Oxygen saturation at baseline: 95.4, during: 95.6, and after procedure: 95.2), and for behavioral parameters (Sleep wake pattern at baseline: 1.49, during: 4.70, and after procedure: 4.55), and (for facial expressions at baseline: 0.03, during: 3.65, and after procedure: 3.15) when compared with control group For Physiological parameters (HR at Baseline: 144.07, during 160.23, and after procedure: 174.75), (Oxygen saturation at baseline: 95.38, during: 95.30, and after procedure: 91.10), and for behavioral parameters (Sleep wake pattern at baseline: 1.68, during: 5.50, and after procedure: 5.70), and (for facial expressions at baseline: 0.19, during: 4.95, and after procedure: 5.45).[32]

Music therapy decreases pain in term neonates during BCG vaccination.[33] To verify this, 50 full-term neonates with birth weight > 2500 g, and gestational age between 38-40 weeks were recruited in the study. Neonates were randomly allocated into three groups.[33] Neonates in Group A received no intervention; Group B received Vocal music (Rockabye) played at 60 dB by sound meter app, and Group C received Piano music played at 60 dB by sound meter app. Physiological, behavioral parameters, and NIPS were used as an outcome measures. Outcomes were taken through Vedio recording at the baseline before starting the music, and continued during the procedure. Music was started after collecting the baseline parameters, and continued throughout the procedure.[33] The study results showed that mean NIPS scores were decreased in Vocal music group (3.47) when compared with Group A (4.69) and C (4.47). Vocal music decreases pain in term neonates during BCG vaccination.[33]

2.8. Sensation development and mechanism of action

Touch is the very first sensation developed around 15 weeks of gestation. During NICU stay, neonates are deprived of touch sensation.[34] Skin to skin contact with massage reduces stress behaviors and improves weight gain in hospitalized neonates. *Auditory sensation* develops between 25-27 weeks of gestation. In this fetus can identify low frequency sounds such as heartbeat of mother and her speech.[34] Auditory sensation helps in generating memory and strengthening the neurological connections in the regions of cortex and limbic system. *Visual sense*[34] starts developing around 24 weeks and achieves functional maturation around 32 weeks of gestation. It also enhances the auditory processing in neonates. Visual stimulation[34] is given with black and white

cards at 20-25 cm distance, because they neonates are attentive to these colors only at the time and after birth.

Olfactory sensation develops around 28-32 weeks of gestation.[34] There is a strong connection between emotional processing and olfactory stimulation. It also generates memory and learning. Olfactory stimulation given with maternal odor and other odors such as lavender and vanilla (artificial or natural self-extracted) ameliorate mood regulation and emotional distress, further produces calming effects among neonates.[35] Olfactive stimulation with familiar odor (breast milk/vanilla) is associated with less crying during minor painful procedure.

Vestibular sense is well developed around birth.[34] Vestibular sensations are associated with perception of movement, spatial memory, occulomotor and postural control which are influenced by gravity. Normal tone development is attributed by the effect of vestibular stimulation in neonatal period. Vestibular stimulation given in hammock positioning develops flexor tone in preterm neonates.[36] It is also given in gently in horizontal and vertical rocking position. It helps in development of flexor tone which reduces the incidence of secondary complications among hospitalized neonates. *Oral stimulation* given in perioral and intra-oral structures helps in promoting oral sensation among neonates.[10] MSS shows improvement in social interaction, habituation, state organization, reflexes and motor system. It also helps in decreasing procedural pain due to release of anti-stress hormone- Oxytocin.[37]

2.9. Multisensory stimulation in reducing procedural pain

MSS is believed to act through two mechanisms: decreased inhibition due to mild stimuli (massage and oral) inducing activation of the inhibition pathway and production of endorphins; and inhibits pain-inducing stimuli in the spine of cord, through median neurons that act as a pain-inducing gate, known as "gate control". The MSS has been described with names other eg "Multisensory stimulation", "Sensory saturation". The aim of this article was to review the available evidence for MSS and to assess its analgesic efficacy in term and preterm infants.

MSS helps in reducing procedural analgesia in term neonate. To identify this, total 120 term neonates between 38-41 weeks of gestation underwent heel pricking.[38] Term neonates were randomly allocated into six groups (17 each). Neonates in one group received no intervention, in another group received 1 ml 33% oral glucose with syringe to stimulate sucking for 30 seconds before 120 seconds of heel prick, in third group, neonates received 1ml of distilled water with syringe to stimulate sucking for 30 seconds before 120 seconds of heel prick, in fourth group neonates received 1 ml 33% oral glucose and sucking, in fifth group neonates received multisensory stimulation (Kinesthetic, visual, tactile, auditory, and olfactory) along with 1 ml 33% oral glucose and in sixth group MSS with 1 ml of distilled water was given. Procedural pain was assessed with Douleur Aigue du Nouveau-ne (DAN) Scale. This pain scale evaluates facial grimacing, limb movements, and vocal expression. Neonate’s reactions were recorded with a SONY Vedio camera from 30s prior to 30s after painful procedure. Along with pain, behavioral state of neonates was also noted. The study results reported significant decrease in DAN score in group A, C, D, and E ($p< 0.0001$). Range

of DAN scores in group A and up to group E was 1-4, whereas in group F from 2-5. As the data was given in graphical representation, the objective values were not available. Among all, pain scores were decreased in group E (MSS along with 1 ml of 33% of oral glucose). MSS given along with oral sucrose was more effective analgesic technique as compared to other treatment procedures given in the other groups. MSS potentiates the effects of oral glucose when given in combination.[38]

Sensorial saturation (SS) is more effective in relieving neonatal procedural pain than unimodal analgesia.[39] To determine this, 108 neonates > 32 weeks of gestation with minimum postnatal age of 48 hrs. were recruited in the study. The neonates were randomized into three groups. Neonates were undergone for venipuncture blood sampling procedure. Neonates in group A received SS along with sucrose, 30 seconds before starting the procedure, nurses started talking with the neonate, looked into neonate's eyes, gently massaging the cheeks, and other areas of the neonatal face along with 24% sucrose administration. Neonates in group B received SS along with 24% breast milk, however procedure is similar, sucrose was replaced with breast-milk. Neonates in group C received an oral sucrose of 24% only. Pain intensity was measured by Premature infant pain profile-Revised (PIPP-R). Along with pain, behavioral and physiological parameters were also assessed. Outcomes were assessed 30s before and throughout the sampling procedure. The outcomes were assessed with stopwatch to document the duration of behavioral parameters. Physiological parameters (HR, and oxygen saturation) were assessed with neonatal Oximeter. The study results revealed that intensity of pain in Group A (2.222 ± 1.098) and Group B (2.028 ± 1.055), (p= 0.001) were lowest when compared to Group C

(5.222 ± 1.290). The study findings concluded that SS given along with sucrose and breast milk is more effective than unimodal (24%) oral sucrose.[39]

MSS also helps in reducing stress and pain in preterm neonates undergoing eye examination.[35] To verify this, 80 preterm neonates < 32 weeks, and birth weight between 1500- 2000 g were recruited in the study. Preterm neonates were divided into experimental and control group.[35] In experimental group, MSS (Visual, taste, tactile, and olfactory stimulations) were given 15 min. prior to the eye examination, while control group was received routine NICU care only. In experimental group, neonates received Visual stimulation: neonate's mother asked to look into the eyes of neonate and try to attract the neonate's attention, In Tactile stimulation: mother was asked to massage (stroking) face, upper limb, and lower limb of the neonate. In Auditory stimulation: Mother was asked to speak with her neonate continuously. In olfactory stimulation: Vanilla essence was used with a sterile gauze piece contains 0.64 g of vanilla diluted in 100 ml of distilled water and placed closed to neonatal nostrils at the distance of 1-2 millimeters, and In oral stimulation: 1ml of 33% of glucose was administer through syringe into the mouth of the neonate without needle for 30sec to induce sucking.[35] This stimulation was given for 2 min. prior to the eye examination, while other sensory stimulations were given 15 min. prior to the examination. Pain and physiological parameters was taken as outcome measures. The pain intensity was recorded with PIPP scale. PIPP scoring was performed by the blinded individual by watching the Vedio. Physiological parameters, behavioral parameters, and pain severity was scored with vedio recording performed for three times: before, during, and after eye examination.[35] The pain was assessed at the 7 stages of 30 seconds: Before 30 sec of

first eye examination, during 30 sec. of first eye examination, at the end of the first eye examination for the 30 sec., again 30 sec. before beginning of the second eye examination, during 30 sec. of the second eye examination, 30 sec. at the end of second eye examination, 30 sec. after the end of eye examination, again after 30 sec. of eye examination for 6 to 7 minutes. The time duration of each eye examination was also recorded using chronometer, each eye examination requires 30-45 sec. The results showed no significant differences in demographic characteristics (gender, birth weight, adjusted age, gestational age) among both the groups. Experimental group shows significant changes (decrease in pain scores), at initial examination (11.0±3.2), and after 1 min. of the procedure (9.3±3.7) when compared with control group, at initial examination (13.5±3.5) and after 1 min. of the procedure (10.5±3.5).[35] Average mean of pain scores were less during the 7 stages of eye examination when compared with the control group. The study results concluded that MSS helps in reducing pain caused due to eye examination to screen retinopathy among preterm neonates. Therefore, MSS is considered as standard of care in reducing pain and stress among preterm neonates undergoing retinopathy screening.[35] There is definite need of scoping or systematic review in the area of Neonatal and Pediatric pain management, to know the currents trends of practices in procedural pain management.[40]

2.10. MSS in improving neurobehavioral outcomes

MSS improves neurobehavioral responses in high risk preterm neonates.[17] To analyze this, 40 high risk preterm neonates with 32 to 26 weeks of gestation, and between 1000 to 2000 g birth weights were recruited in the study. They were selected based on the New Ballard score and mean gestational weight, and allocated in either control group or

study group. The control group received routine NICU care, whereas study group received MSS program given 45 minutes for daily 2 weeks. Neonates in MSS group received: Tactile stimulation with gentle massage. Stroking was given with moderate pressure from head and neck followed by upper and lower limbs, and then back for total 10 minutes. Six strokes were administered to each body part, and each stroke was lasted for 10 sec. Vestibular stimulation was given in hammock supine position. Kinesthetic stimulation was also given in supine position consisted of passive range of motion exercises of upper and lower limbs. Auditory stimulation was given with recorded maternal voice. Oral stimulation was administered by gently stroking cheeks, lips, and jaw by middle and index fingers for 7 min., and stroking of intraoral structures such as gums and tongue with moderate downward pressure. Along with oral stimulation, NNS were also provided. Each stimulation was provided for 5 min. inside the incubator. Neonatal neurobehavioral and neuromotor assessment was taken as an outcome measure along with weight gain. The outcomes were assessed at the baseline and after 2 weeks of intervention. Neonatal neurobehavioral examination was performed by Morgan neonatal neurobehavioral examination (MNNE) and Brazelton neonatal behavioral assessment scale (NBAS). MNNE scale is consisting of total 27 items. Each item of the scale is scored with three-point system. NBAS consists of 28 behavioral items and 18 reflex items. Behavioral items are score on nine points (0 to 8), while reflex items are scored on four points (0 to 3). The study results showed no significant difference ($p>0.05$) between the groups at pretreatment, while pretreatment and post treatment significant difference were noted within experimental group ($p<0.05$) in measured variables except in autonomic system and State regulation. In control group,

no significant difference was noted except in weight gain. Post group comparison shows statistically improvement in both the groups ($p<0.05$), except for state regulation, weight gain, and physiological parameters. The study findings highlights that MSS helps in improving neonatal neurodevelopment along with weight gain in high risk infants, and also acts as a vital part of routine neonatal physiotherapy care in NICU.[17]

MSS shows beneficial effects in neuromuscular development of preterm neonates.[41] To document this, 80 preterm neonates were randomly allocated into two groups (40 in each). The preterm between 32 to 36 weeks of gestation were recruited. In experimental group MSS was given for 12 min. daily, 5 days per week after 48 hrs of birth while in control group routine NICU care was only given. MSS consisting of Auditory, tactile, visual, and vestibular sensation each was given for 3 min. Auditory stimulation was given with soft lullaby (between 30-40 dB) through miniature speaker, tactile stimulation was given with gentle stroking in a sequence of chest, upper extremities, and lower extremities in supine position. Visual stimulation was given with black and white stimulation cards kept at a distance of 8-10 min., and Vestibular stimulation consist of horizontal and vertical rocking was given to the neonates. The neuromuscular development was assessed with New Ballard Score at the baseline and after 5 days of intervention. Total score was ranged from 0 to 25. Total five criteria are scored. Four criteria are ranged from 0 to 4, while one criterion is scored from 0 to 5. The results of the study showed no significant difference in demographic characteristics (gestational age, birth weight, height, length, and head circumference) between the groups. In experimental group, scores were increased (at baseline: 15.2±2.2, and post treatment: 23.7±1.9) as compared to control group (at baseline: 14.8±2.5, and post

treatment: 18.1±2.4). Significant difference was noted between both the groups before and after intervention (p=0.001). The study concluded that MSS has beneficial effects on neuromuscular development on preterm neonates. It could acts as an integral part of neonatal physiotherapy among preterm neonates.[41]

MSS showed improvement in neurodevelopmental maturation among preterm neonates.[36] To determine this, 50 preterm infants born between 28-36 weeks of gestation, and birth weight ranging from 1000-2000 g were recruited for this trial. The New Ballard Score was used for baseline assessment of neuromuscular maturity in preterm neonates. The control group received routine NICU consisted of KMC and breast feeding, while MSS was given in experimental group for 12 min., 5 days per week discharge from the hospital. MSS consisting ATVV (Auditory, Tactile, Vestibular, and Visual) stimulations were given. Auditory stimulation was given with soft lullaby between 30-40 dB through miniature speaker, and an mp3 player for 3 minutes. Tactile stimulation consisted of gentle stroking given for 3 min. in the sequence of chest, followed by upper and lower limbs in supine position. Visual stimulation was also given for 3 min. with black and white cards hung at a distance of 8-10 in. from the eyes of the neonate. Vestibular stimulation was also given for 3 min. comprised of gentle horizontal and vertical rocking. MSS was given after 48 hrs. of birth. During intervention, physiological and behavioral stress signs were recorded with multi-parameter monitor. INFANIB was taken at the term age of preterm neonates. INFANIB consists of 20 items, which assess the neonate's motor development. The trial results highlighted statistically significant differences between the groups (p<0.005). In experimental group (at baseline: 22.4±6.1, and post treatment: 62.24±3.07) scores improved compared to

control group (at baseline: 23.9±5.7, and post treatment: 59.16±3.23). The study concluded that ATVV appears to have immediate positive effects on neurodevelopment at their term age. It can also consider as important part of the regular neonatal physiotherapy for healthy preterm neonates.[36]

2.11. Soft tissue therapy/ Massage therapy as an analgesic

Touch is the fastest and first most develops during and after birth. It is important for developing preterm neonate, who is deprived of gentle human touch during NICU stay.[42] Soft tissue therapy improves neonatal weight, height and circumference, vital signs, feeding volume, skin fold thickness and motor performance.[43] Till now, many studies have not specified the relationship between STT and pain among neonates, but have association with developmental indicators. Massage given in combination with other non-pharmacological therapies such as given in combination with breastfeeding, non-nutritive sucking, and oral sucrose helps in managing procedural pain.[44] The moderate pressure evokes parasympathetic response as compared to light touch, which elicited a sympathetic response.[44] It enables the release of endorphin and encephalin by stimulating pituitary gland through massage and reflex pints in the joints. It has similar effects on reducing cortisol levels.[44]

Foot massage prior to the intervention decreases pain intensity, and improves physiological and behavioral stability in preterm neonates. To examine this, a pilot study was conducted.[45] Total 120 preterm neonates < 32 weeks of gestation, and birth weight < 2500 g were included in the study. Neonates were randomized into experimental and control group (60 in each). Neonates in experimental group have not received massage

during first sampling procedure but received 15 min. foot massage prior to heel stick after 3 days.[45] Prior to the procedure, massage was given over the outer aspect of leg from toes to mid thigh by using firm gentle pressure by fingers and thumbs. Massage consisted of 5 minutes of tactile stimulation, followed by kinesthetic stimulation for 5 minutes, and wending again with tactile stimulation for 5 minutes. Control group received no intervention. For measuring pain intensity, PIPP scale was used as an outcome measure. PIPP was taken 5 min. prior to the procedure, during and after the procedure. Measurements were taken on day one, when massage was not administered, and after 3 days. Physiological and behavioral components of PIPP score were recorded with Philip's monitoring system and neonatal pulse Oximeter. The study results revealed that massage increases HR before procedure, but HR decreases after the procedure. Neonates in experimental group have stable behavioral outcomes, statistical significant difference (p=0.001) were noted in experimental group when compared to control group.[45] The PIPP mean scores were lowered in experimental group after receiving massage (p=0.001). Pain severity also decreases in experimental group; neonates have moderate pain after receiving massage. The study results also revealed no correlation between PIPP scores and demographic characteristics (day of admission, gestational age, sex, height, birth weight).[45]

A RCT consisted of 75 neonates with the gestational age > 34 weeks, and birth weight up to 3000 g was recruited in the study.[46] 75 neonates were allocated into three the groups (25 in each). In Group A, neonates received breastfeeding; this was continued up to 3 min. after that venepuncture was done. In Group B, massage (stroking and effleurage) was administered on procedural site for 3 min., after that procedure was

performed.[46] In Group C, no intervention was given to the neonates. During the procedure, NIPS was recorded with Parasonic handy cam. Recorded films were observed by the independent reviewers. NIPS Scoring was taken at 30 s before, beginning, during, and after the procedure. The study results showed no significant difference in demographic characteristics ($p<0.05$) (gender, birth weight), except for gestational age ($p>0.05$). Mean pain scores were decreased in massage group (0.92), breastfeeding breast feeding (6.16), and control group (4.84). The study concluded that massage improves procedural pain caused by venipuncture better than breast feeding.[46]

Massage therapy helps in improving behavioral, physical, and physiological state, weight gain and reduces length of stay in preterm neonates admitted in NICU.[47] To determine this, Preterm neonates with 32-36 weeks of gestation, and birth weight < 2500 g were included in the study. In this quasi-experimental study, preterm neonates received massage therapy in the sequence of tactile stimulation (5 min.) followed by kinesthetic stimulation (5 min.), and ended by tactile stimulation (5 min.) again. Massage therapy was given two times a day for 15 minutes, up to 5 days of NICU Stay. After massage therapy, preterm neonates were assessed for vital signs (temperature, RR, HR) with premature neonate's massage observation sheet, pain was assessed with NIPS, and weight gain along with length of hospital stay was assessed at the day of discharge. The outcomes (physical, behavioral, physiological state, and pain) were measured at the baseline and every day after painful procedure.[47] The study results showed significant difference within the group. Significant difference was also noted in physiological state, and behavioral state pre and post massage therapy. Procedural

pain decreases after applying massage therapy, and significant difference was also noted. Weight gains were also increased, whereas length of stay decreases. The study concluded that massage therapy helps in improving physical, physiological, and behavioral state along with pain in preterm neonates between 32-36 weeks of gestation undergoing painful procedures.[47]

2.12. Neonatal pain assessment scales[22]

There are various types of reliable and valid assessment tools for measuring neonatal pain, stress and discomfort in different clinical practice settings.[48] Neonates are commonly having procedural and postoperative pain during their hospital stay. Some common assessment tools used for measuring procedural and postoperative pain among neonates and infants are Premature infant pain profile (PIPP), Neonatal infant pain scale (NIPS), CRIES scale, Neonatal pain agitation and sedation scale (N-PASS), and COMFORT scale.[48] These assessment tools helps in measuring parameters such as behavioral state, activity, alertness, calmness, respiratory distress, muscle tone, facial distress, and heart rate among neonates and infants. Many literatures showed that the pain control in the neonatal period is helpful in assessing pain and managing improving behavioral, hormonal and the physiological outcomes. By avoiding painful interventions the neonatal pain can be managed effectively.[13]

2.12.1. Premature infant pain profile (PIPP)

PIPP was developed specifically for the assessment of acute pain in premature and full-term infants.[13] PIPP is a composite measure of 7 indicators that includes behavioral, physiological and contextual indicators. These 7 indicators were reviewed by a panel of

multidisciplinary experts who established the validity of the content. The 7 indicators include: gestational age; behavioral state; heartbeat; Oxygen saturation; puffy eyebrows; eye pinch; and naso-labial folds. Each PIPP index was assessed on a 4-point scale (0, 1, 2, and 3) with a possible total score of 1821, depending on the gestational age of the infant. To date, PIPP has been validated in a number of studies using synchronous Vedio recording of behavioral cues (i.e. facial expressions) and computer acquisition of physiological cues (frequency heart rate, oxygen saturation) to enable slow motion data analysis in seconds. Using these methods, good inter- and internal reliability (> .90) has been consistently demonstrated in all studies.[13]

2.12.2. Neonatal Infant Pain Scale (NIPS)

Lawrence and colleagues developed NIPS, a six-item scale, based on the results of surveys of 43 experienced neonatal nurses working at Eastern Ontario Children's Hospital.[49] Nurses were asked to identify behaviors related to varying degrees of pain and distress in premature and full-term infants who responded to pain procedures. They identified 6 types of behaviors in this population: facial expressions, types of crying, breathing patterns, arm movements, types of leg movements, and types of arousal states. Crying has three response categories (0, 1, 2); the other behaviors have two (0, 1). The total score ranges from 0 to 7, and higher scores may indicate pain. Pearson's correlation is used to calculate mutual confidence of the total NIPS score 0.92-0.97. These identical episodes out of 20 were used to demonstrate the concurrency efficacy of using Pearson's correlation. The correlation between NIPS and the visual analog scale (VAS) ranges from 0.53 to 0.84 is similar to the correlation between VAS obtained

by two independent observers. The authors suggested that the behavioral response score increased during the procedure and then decreased after the procedure.[49]

2.12.3. Crying requires oxygen increased administration, increase in vital signs expression sleep (CRIES) Scale

Another infant pain rating scale, CRIES, developed at the University of Missouri at Columbia, was specifically developed as a reliable and valid scale for measuring infant pain response in the postoperative period.[49] A score of 4 or more indicates pain and requires intervention. Twenty-four postoperative children, aged 32 to 60 weeks postoperatively, were included in the study. Inter-rater reliability was 0. 72 were proven using the Spearman correlation coefficient. A concurrent validity test with Older Infant pain scale (OPS) was performed using the Spearman correlation coefficient and the 0.73 coefficient has been shown. These results suggest that CRIES is a reliable and valid measure of neonatal postoperative pain.[49]

2.12.4. The COMFORT-B Scale

The COMFORT-B scale includes six behavioral items: alertness, calmness, respiratory response (for mechanically ventilated infants) or crying (for spontaneously breathing infants), body movements, facial tension, and muscle tone for individual items of the COMFORT-B scale.[50] The mean Kappa was 0.79 for 122 nurses [interquartile range (IQR) 0.72-0.86]. The internal correlation for the total COMFORT-B score was 0.96. A kappa coefficient of 0.65 or greater is considered to reflect sufficient confidence between sets.

2.13. Neonatal neurodevelopmental outcomes

2.13.1. The International Neonatal Neurological Battery Test (INFANIB)

The INFANIB monitor tool includes 20 items that assess the condition of the infant in lying, lying, sitting, standing and hovering for body tone and posture, primitive reflexes and French angles from 4 to 18 months, this method is suggested by Ellison et al. (1985), and was used as a screening test, due to its high validity and reliability.[36] INFANIB can also be presented as a valid test against the Children's Developmental Inventory (sensitivity = 75%, specificity = 70%), parental assessment of developmental status (sensitivity = 74 to 79%, specificity = 70 to 80%), Bayley Newborns Neurodevelopmental screening questionnaire, age and stage (sensitivity = 70-90%, specificity 76-97%). In addition, the intra-correlation coefficient was 0.90.[36]

2.13.2. Test of infant motor performance (TIMP)

TIMP is a 25- 35-minute motor outcome measurement typically performed to assess postural and selective movement control required by neonates under four months of age.[51] The TIMP was developed to identify children with developmental delays, discriminate among children with varying degrees of risk for poor motor outcomes, and measure change due to the intervention. It is used by physiotherapists and occupational therapists to identify children with developmental delays from 34 weeks especially to 5 months postpartum and to plan intervention programs and document changes in performance over time. TIMP can be used both in special care settings and in early intervention programs, thus facilitating the exchange of information between caregivers in different settings. TIMPSI retest reliability is excellent with an internal factor of 0.99.[51]

2.13.3. The Neurobehavioral Behavioral Assessment of Premature Infants (NAPI)

NAPI provides detailed information on the development of behaviors of premature infants.[52] NAPI is a test developed at Stanford to measure the relative maturation of

premature infants from 32 weeks postmenopausal age (PMA) to term. Elements of Motor Development Group include Abdominal Suspension, Head Raise, Crawl Reflex, Forearm Recoil, Active Movement Power, and Spontaneous Movement Power. Guidance and alertness categories include percentage of time in an alert state, duration and quality of alertness, quantitative responses to visual and auditory stimuli inanimate and inanimate, and qualitative ratings represent the nature of responses.[52]

2.13.4. The NICU Network Neurobehavioral scale (NNNS)

A full description and user manual for NNNS are available. It includes information on scoring, analytical techniques and training requirements.[53] In short, the NNNS is a comprehensive assessment of neuronal integrity and behavioral function, including markers of stress. It fully assesses neonatal neurobehavioural activities (orientation towards auditory and visual stimuli); nervousness in newborns (color change, tremors, and startle), nervous activity (reflexes, tone); some characteristics of gestational age; self-soothing ability; States and their organizations. The neurobehavioral, reflex and stress categories that make up the NNNS can be viewed as individual categories, but based on their large number, 13 points of synthesis (i.e., orientation, habit, preference and preference). Coma, suboptimal reflexes, asymmetric reflexes, stress, self-regulation, motor quality, treatment) are often used to summarize clinical examination and used for statistical analysis in studies (see below for development of neurobehavioral profiles). From a procedural standpoint, it oversees the assessment of neurobehavioral categories within States, the independent management of the different categories, as well as the institutional and regulatory review of States. It can be used for small and very large neonates once they are stable and well in the postpartum period.[53]

The internal consistency of NNNS was assessed by Tronick and colleagues. They found that Cronbach's alpha fluctuated between 0.87-0.90 for composite scores.[53]

2.13.5. Premie Neuro

Preterm neonates are more prone to motor cognitive delays because of NICU stay. Very preterm neonates (< 32 weeks) experience motor and cognitive impairment. Early identification of developmental delays is very important to decrease the risks of future morbidity.[54] Neurobehavioral evaluations performed during NICU stay predict long term disability among preterm neonates. Early brain imaging and assessment of neurobehavioral status predicts motor and neurodevelopmental delays. The Premie-Neuro is a neurological examination tool for preterm neonates between 23 to 37 weeks of gestation. It consists of total 24 items. It has 3 main components: neurological, movement, and responsiveness examination. A neurological examination component addresses reflexive behavior, progression of muscle tone, and movement type. 2nd factor documents rate of avoidance behavior and limb movement. Responsiveness component address alertness. Total 14 out of 24 items are related to the assessment of motor responses and reflexes, other 10 out of 24 items evaluates stress signs, and other behaviors (excitability, and arousal). The score range of Premie-Neuro lies between 24 and 120. Raw scores obtained from the data and categorize neonate’s performance into abnormal, questionable or normal. Preterm neonates less than 28 weeks of gestation who requires ventilation or intubated are scored on the basis of 16 items, 8 items on reflexes and motor responses, and other 8 items on behavior. This scoring form designed for neonates less than 28 weeks of gestation, and is known as abbreviated form. Raw scores are obtained from the data and ranged between 16 to 80,

which can be categorized into abnormal, questionable or normal. Premie Neuro is easy to administer, and can be learned easily by reading a manual through clinical practice.[54] It takes approximately 5 minutes to administer the standard form and 1-2 min. for abbreviated form. The intra-class correlation coefficients (ICC) for inter-rater reliability is 0.39-0.55, and for test-retest reliability (1 day) is 0.49 – 0.59. It has poor inter-rater reliability and fair to moderate test-retest reliability for combined test.[55] ICC for inter-rater reliability for movement and neurologic subtests is 0.556, and test-retest is 0.493.

Very preterm neonates experience many stressful events, which are occurring at the time of rapid brain growth development and organization.[56] These stressful events influence cortical connectivity which leads to abnormal brain development. Routine medical care provided by nurses and standardized neurobehavioral assessments causes' environmental stress to the neonate. For preterm neonates, it is very difficult to limit the exposure of these environmental stressors at same time of providing essential care. To determine the association between physiological stresses of very preterm neonates undergoing medical procedures and neurobehavioral assessments leads to additional stress on preterm neonates. To determine this, 34 preterm neonates between 29-34 weeks of gestation were recruited in the study.[56] The physiological stress imposed by neurobehavioral assessment and routine medical procedures was compared with each other. There standardized neurobehavioral assessments were carried out with the general movement assessment (GM), The Hammersmith neonatal neurological examination (HNNE), and the Premie-Neuro were administered weekly from birth to 32 weeks of gestation. Assessments were taken together with routine medical care provided by the nurses and continued up to ongoing daily care. Both the

procedures were recorded with Video camera kept above the incubator. Neonatal physiological parameters were also recorded at the time of administration of both the procedures. Videos were analyzed by independent researcher blinded to the procedures.[56] The main physiological parameters recorded were Heart rate (HR), and Oxygen saturation (SPo_2). These physiological parameters were compared between these procedures. The study results showed that Neurobehavioral examination was related with low mean HR compared to routine medical care (mean difference= 5.9). On other side, SPo_2 was higher during neurobehavioral assessment as compared to routine medical care (mean difference= 2.5%). The study results concluded that neurobehavioral assessments cause less physiological stress than routine medical care among preterm neonates between 29 to 32 weeks of gestation.[56]

2.13.5.1. Premie-Neuro and other clinical biomarkers

Brain imaging and clinical examination are two different techniques to identify anatomical and physiological markers of brain injury in neonates to predict future outcomes.[57] To explore this, one study recruited preterm neonates less than 31 weeks of gestation. Brain MRI was performed two times between 30 and 32 weeks of GA (preterm age) and again at 40-42 weeks of GA (Term age). Same week, clinical outcomes were also taken with Assessment of General movement (GM), HNNE, NNS, and Premie-neuro at preterm, and term age. TIMP and Visual assessment were also taken around Term age. Multivariable regression analysis was used to find the association between early MRI and clinical measures. The results showed strongest association between cerebellar scores and HNNE reflexes, NNNS Hypertonicity, and Subscales of Premie-Neuro neurological component. Cortical scores were associated

with HNNE subscales of posture and tone, and subscales of regulation and hypotonicity of NNNS. Multivariable regression analysis was used to find the association between Term MRI and Clinical measures.[57] The results showed white matter scores were associated with the TIMP, Abnormal signs under HNNE, and NNNS hypertonicity. Cortical scores were associated with tone patterns, orientation, and behavior components of HNNE. Cerebellar scores were associated with posture and tone components of HNNE, and Hyper-hypotonicity components of NNNS. Global scores were associated with TIMP, abnormal signs of HNNE, and NNNS Hypertonicity. The study concluded that at early MRI, cerebellar scores have strongest relationship with clinical measures. They are more related to neurological and motor component as compared to behavioral items. At Term MRI, the strongest relationship was found with motor performance with the TIMP.[57]

Same authors performed similar study, they took MRI and clinical assessments alone and also in combination from early (<31 weeks of gestation), at term age, at 3 months of corrected age, and again around 2 years of corrected age.[58] 98 preterm neonates were enrolled for this prospective cohort study. As similar like previous study, MRI and clinical assessments were taken at early age, term age, at 3 months of corrected age, and around 2 years of corrected age. In this study outcomes used at 3 months of corrected age were General movement assessment, TIMP, and visual assessment. Around 2 years, outcomes used were Bayley scale of infant and toddler development 3rd edition. MRI was taken at early and term age only. Premie-neuro has no association with motor outcomes, while reflexes component of HNNE shows association with motor outcomes along with NNNS at term age. TIMP scores and visual assessment scores were also

showed association with motor outcomes at 3 months of corrected age. Whereas, Premie-Neuro scores (neurological component) were associated with cognitive outcomes, along with subcomponents of HNNE (reflexes), NNNS (Arousal and stress) at early age. Term HNNE (posture, and tone, tone patterns, spontaneous movements, reflexes, and total score), Term NNNS (regulation), TIMP, and visual assessment, also 3 months TIMP, and visual assessments were also showed relationship with 2 year cognitive outcome.[58]

Medical and environmental factors during NICU stay can have impact on neurobehavioral outcomes and development in preterm neonates.[59] To verify this, 88 preterm neonates less than 30 weeks of gestation were recruited in the study. Neurobehavioral assessment was taken within 14 days of NICU Stay.[59] Assessments were taken at 30 weeks gestation and between 37-41 weeks of gestation. Neurobehavioral assessments were taken with Premie-Neuro, at 30 weeks of gestation, while NNNS and HNNE were taken at term age. The study results showed low premie-neuro scores at 30 weeks. Low premie-neuro scores were associated with low birth weight, presence of Patent ductus arteriosus (PDA), endotracheal intubation, and administration of oxygen therapy. No association was found between baseline and medical and environmental factors related to neurobehavior at 3o weeks of gestation. Multivariate analysis shows low premie-neuro scores at 30 weeks of gestation and was related to low HNNE scores at term and NNNS (movement, suboptimal reflexes, stress, asymmetry, and excitability), after controlling the medical and environmental factors.The study concluded that neurobehavioral assessments scores taken with Premie-Neuro at 30 weeks were associated with HNNE and NNNS at term age.[59]

2.13.5.2. Premie-Neuro examination procedure[54]

Examination should be conducted before half hour from feeding. Time must be recorded before starting the procedure, and throughout the procedure.

Factor 1: Neurological

2.13.5.2.1. *Component 1: Arm recoil*

Position of the neonate: Supine

Procedure: Hold the neonate from both the forearms and extend the elbows and release them immediately. Observe the amount of flexion around both the elbows within 2-3 sec.

2.13.5.2.2. *Component 2: Arm traction*

Position of the neonate: Supine

Procedure: Hold the neonate from wrist, and pull neonatal arm vertically. Perform it each side separately.

Note elbow flexion, note it for few seconds after shoulder is off the surface of incubator.

2.13.5.2.3. *Components 3: Palmar grasp*

Position of the neonate: Supine

Procedure: Insert index finger towards the neonatal ulnar side of neonatal hand and gently press the palmar surface with index finger.

Grade the finger flexion according to the strength. Repeat the procedure with other hand.

2.13.5.2.4. *Component 4: Plantar Grasp*

Position of the neonate: Supine

Procedure: Pressure will be given from thumb to the ball of neonatal foot.

Grade the toe flexion according to the strength.

2.13.5.2.5. *Component 5: Scarf sign*

Position of the neonate: Supine

Procedure: Hold neonatal arm near from the elbow and move across the neonatal chest until resistance not felt. Observe and note the angle formed between upper arm and an imaginary line parallel to the trunk.

2.13.5.2.6. *Component 6: Popliteal Angle*

Position of the neonate: Supine

Procedure: Extend both the legs by applying gentle pressure behind the ankles until resistance not felt. Measure the angle between upper and lower parts of the lower limbs. Repeat the procedure with another arm.

2.13.5.2.7. *Component 7: Heel to ear*

Position of the patient: Supine

Procedure: Hold neonatal feet together from the ankles, hips should be in neutral, and knees extended. Bring heel towards the ear, until resistance not felt. Measure and note the angle between neonatal trunk and leg.

2.13.5.2.8. *Component 8: Movement Type*

Identify the type of movement happening during the procedure: Sluggish, jerky, uncoordinated, or smooth. Observe the type of movement throughout the procedure.

For 9-16 items, determine rate/time based on the number of observations by total time taken for completion of the procedure

2.13.5.2.9. *Component 9: Tremors*

Note the no. of episodes observed in any body part (face, and extremities)

2.13.5.2.10. *Component 10: Thrashing*

Note the no. of episodes (flailing movements, overshooting) observed in any body part (Head and trunk, extremities)

2.13.5.2.11. *Component 11: Facial Grimace*

Note the no. of facial movements observed during the examination

2.13.5.2.12. *Component 12: Startle*

Observe the neonate for sudden response (flexion or extension) of the arms and legs in response to stimulus given through bright light or a loud noise. Note the number observed during the procedure.

2.13.5.2.13. *Component 13: Yawn*

Note the no. of yawns observed during the procedure.

2.13.5.2.14. *Component 14: Color change*

Note any skin color changes observed during the procedure, and record the number.

2.13.5.2.15. *Component 15: Arm movements*

Note the no. of spontaneous movements observed during the procedure.

2.13.5.2.16. Component 16: Leg movements

Note the no. of spontaneous movements observed during the procedure.

2.13.5.2.17. *Component 17: Arm Flexion*

Position of the neonate: Supine

Procedure: Hold both the wrists and apply gentle traction, continue and bring neonate in sitting position. Note flexion at the elbow just before lifting the neonate.

2.13.5.2.18. *Component 18: Head Lag*

Position of the neonate: Supine

Procedure: Hold both the wrists and apply gentle traction, continue and bring neonate in sitting position. Note the amount of head lag.

2.13.5.2.19. *Component 19: Held sit*

Position of the neonate: upright sitting position

Procedure: Note the length of time the head is held in midline upright position.

2.13.5.2.20. *Component 20: Posterior neck*

Position of the neonate: Upright seated position

Procedure: Observe neonatal head to fall forwards as hold from the shoulders and wait for 15 seconds. Note the neonate's ability to lift and hold the head in midline upright position.

2.13.5.2.21. *Component 21: Anterior neck*

Position of the neonate: Upright seated position

Procedure: Observe neonatal head to fall forwards as hold from the shoulders and wait for 15 seconds. Note the neonate's ability to lift the head in midline upright position.

2.13.5.2.22. *Component 22: Alert*

Position of the neonate: Upright position

Procedure: Note the total amount of time, the neonate is in quiet and in alert state

2.13.5.2.23. *Component 23: Ventral suspension*

Position of the neonate: Ventral suspension

Procedure: Note the curvature of back, flexion at the extremities, and relationship of head to the trunk

2.13.5.2.24. *Component 24: Responsiveness*

Position of the neonate: Supine

Procedure: Neonatal awareness levels are noted, such as responses to touch, handling, movement, noise, and hunger.

Table 2.2: Common scales used for measuring neonatal pain

Scale	Total scoring	Scoring criterion	Reliability and validity
Preterm infant pain profile (PIPP)	21	0 to 3	Inter-rater reliability = 0.93-0.96 Intra rater reliability= 0.94-0.98
Newborn infant pain scale (NIPS)	21	0 to 3	Inter-rater reliability= 0.71-0.96
Neonatal pain agitation and sedation scale (N-PASS)	10	0 to 2	Inter-rater reliability = 0.95 concurrent validity with PIPP Score = 0.83
Crying requires oxygen increased administration, increase in vital signs expression sleep (CRIES) Scale	10	0 to 2	Inter-rater reliability= 0.97-0.98
COMFORT-B Scale	35	1 to 5	Inter-rater reliability= 0.71

Table 2.3: Studies related to MSS and STT in improving procedural pain and neurobehavioral development

Authors	Country	Objectives	Target Population	Intervention	Outcomes	Findings
Carlo Valerio Bellieni et al (2002)[18]	Italy	To determine effects of MSS on procedural analgesia in term neonates	120 Term neonates (38-41)	MSS with 1 ml 33% oral glucose	DAN scale	MSS potentiates the analgesic effects of oral glucose
Parimala Suganthini Kanagasabai et al (2013)[36]	India	To determine effects of MSS on neuromotor development	50 preterm neonates (28-36 weeks)	MSS for 5 days	INFANIB	Improves total maturation among preterm neonates
Hossein Zeraati et al (2016)[35]	Iran	To determine effects of MSS during eye examination	80 Preterm neonates (32-36 weeks)	MSS prior to procedure	PIPP	MSS is beneficial during eye screening

Eman K. Mohamed et al (2018)[17]	Egypt	To determine neurobehavioral responses to MSS	40 preterm neonates	MSS for 2 weeks	MNNE NBAS	Improves neurodevelopment along with weight gain
Hossein Zeraati et al (2018)[41]	Iran	To determine effects of MSS on neuromuscular development	80 preterm neonates (32-36 weeks)	MSS for 5 days	New Ballard score	Shows beneficial effects on neuromuscular development
Siti Yuyun Rahayu Fitri et al (2019)[39]	Indonesia	To determine the effects of Sensorial saturation on procedural pain	108 Neonates (> 32 weeks)	SS along with breast milk, Oral glucose	PIPP-R	SS along with breast milk and sucrose is more beneficial than given alone
Ebtsam M. Ibrahim et al (2016)	Egypt	To analyze the effects of foot massage on	120 preterm neonates (< 32 weeks of	Massage was given on foot prior to the	PIPP	Massage decreases pain scores in preterm neonates

		procedural pain among preterm neonates	gestation)	heel prick		undergoing heel prick
Ali Zargham-Boroujeni et al (2017)[46]	Iran	To determine the effects of Massage therapy and breastfeeding	75 neonates (>34 weeks)	Massage in group A, Breastfeeding in group B, No intervention in control group	NIPS	Massage is more effective in reducing procedural analgesia than breast feeding
Orban Ragab Bayomi et al (2015)[47]	Egypt Saudi Arabia	To verify effects of massage on physical, behavioral, physiological state along with pain	Preterm neonates (32-36 weeks)	Massage therapy for 15 min.	Physiological, and behavioral parameters NIPS	Improves physiological, physical, behavioral parameters along with pain and weight gain

Abbreviations: DAN: Douleur Aiguë du Nouveau-né, INFANIB: Infant Neurological International Battery, PIPP-R: Preterm infant pain profile-Revised, MNNE: Morgan neonatal neurological examination, NBAS: Brazelton neurobehavioral assessment scale, SS: Sensorial saturation, MSS: Multisensory stimulation

3. Methodology

3.1. Study design: Two group pretest posttest randomized controlled trial

3.2. Study location: Recognized tertiary care teaching hospital

3.3. Study settings: Neonatal intensive care units (NICU)

3.4. Study participants: Preterm neonates admitted in NICU

3.5. Sample design: Purposive sampling

3.6. Selection criteria:

3.6.1. Inclusion criteria:

3.6.1.1. Preterm neonates of either gender, aged between 30 weeks to 36 weeks and 6 days of gestation

3.6.1.2. Birth weight between 1000 g to 3500 g

3.6.1.3. Not receiving analgesics/sedatives within last 24 hours, Undergoing for painful procedures such as Heel stick/lance, Venipuncture, Arterial puncture, IV cannulation, IV Injection, Finger stick, Lumbar puncture, Gastric tub

insertion, Removal of IV Catheter, Nasal aspiration, Removal of peripheral and intravenous line, Chest Physiotherapy, Suctioning, Removal of adhesive tapes and dressing change

3.6.2. Exclusion criteria:

3.6.2.1. Preterm neonates with congenital malformations

3.6.2.2. Preterm neonates with seizure disorders, intraventricular hemorrhage, Periventricular leukomalacia, requires mechanical ventilation

3.7. Outcome measures:

3.7.1. Preterm Infant Pain Profile-Revised (PIPP-R)

PIPP-R is used to assess acute and prolonged pain in term and preterm neonates. It consists of 7 criteria's and of total 21 scores (0: Minimum Score, >5 moderate Pain, 21: Maximum score). PIPP-R will be taken at the baseline on Day 0 and Day 5 during the procedure. Vedio will be recorded immediately after the painful procedure, at 30 s, 60 s, 90 s, and 120 after the procedure. Based on video observation, PIPP-R scoring will be performed.[26]

3.7.2. Neonatal pain, Agitation and Sedation Scale (N-PASS)

N-PASS is used to measure pain in addition with sedation among term and preterm neonates. N-PASS is consists of five criteria's which are graded as 0, 1 or 2 for pain/agitation, and 0,-1 03 -2 for sedation. The scale has shown an excellent inter-rater reliability (ICC = 0.95) for pain and (ICC = 0.90) for sedation. The concurrent validity with PIPP Score (r = 0.83) for high pain score and (r = 0.61) for low pain score. N-PASS

will be taken at the baseline on Day 0 and Day 5 during the procedure. Video will be recorded immediately after the painful procedure, 30 s, 60 s, 90 s, and 120 after the procedure, PIPP scoring will be performed.[60]

3.7.3. Infant Neurological International Battery (INFANIB)

INFANIB is used for the assessment of neuromotor development for infants aged 0-18 months. It is a 14-item battery for neonates with five criteria's for assessing preterm neurodevelopment which are graded as 05= Normal, 03= mildly abnormal, 01= markedly abnormal. The scale has Intra-class correlation coefficient = 0.90. INFANIB will be measured before the intervention at day 0 and after 5 days of intervention.[61]

3.7.4. Premie Neuro scale

Premie Neuro is neurological examination scale for preterm neonates used for neonates between 23 and 37 weeks of gestation. It has total 24 items (8 in each). Each item has assigned score of 1, 3, and 5. Premie neuro will be recorded before intervention at day 0 and after 5 days of intervention.[55]

3.7.4.1. Components of Premie Neuro

Factor 1-Neurological	Factor 2- Movement	Factor 3- Responsiveness
Arm recoil	Tremors	Arm flexion
Arm traction	Thrashing	Head lag
Palmar grasp	Facial grimace	Held sit
Plantar grasp	Startle	Posterior neck
Scarf Sign	Yawn	Anterior neck

Popliteal Angle Heel to ear Movement type	Color change Arm movement Leg movement	Alert Ventral suspension Responsiveness

3.7.4.2. Scoring can be done according to:

<28 weeks of gestation/ On ventilator: Abnormal: <50, Questionable: 50-90, Normal: 70-80, only first 16 items can be scored because they involve minimal handling.

>28 weeks of gestation/ not on ventilator: Abnormal: <70, Questionable: 70-99, Normal: >100

Table 3.1: Outcome measures for the study

Sr. No.	Scales	Objective	Total score	Age group to be tested	Time Frame	MCID	Reliability and validity
1.	**PIPP**	To assess procedural pain	21	28-40 weeks of gestation	Immediately after the painful procedure around 30s, 60s, 90s, and 120s with video-based observation at day 0 and day 5	02[26]	inter-rater reliability (ICC = 0.93-0.96), and also intra rater reliability coefficients (0.94-0.98)
2.	**N-PASS**	To assess pain along with sedation and agitation	23 (10: Sedation, 13: Pain and agitation)	23-40 weeks of gestation	Immediately after the painful procedure around 30s, 60s, 90s, and 120s with video-based observation at day 0 and day 5	NA	excellent inter-rater reliability (ICC = 0.95) for pain and (ICC = 0.90) for sedation
3.	**INFANIB**	To assess neurodevelopmental outcomes	100	Birth to 18 months of age	At day 0 before intervention and after 5 days of intervention	02[36]	Intra-class correlation coefficient = 0.90

4.	**Premie-Neuro***	To assess neurodevelopmental outcomes	120	23-37 weeks of gestational age	At day 0 before intervention and after 5 days of intervention	NA	Interrater reliability (ICC= 0.391-0.556) Test-retest reliability (0.493-0.592)
5.	**TIMP***	To assess functional motor outcomes	142	32 weeks of gestation to 4 months of age	At day 0 before intervention and after 5 days of intervention	NA	Inter rater-reliability= 0.95, Intra rater reliability=0.99, and Construct validity= 0.85

PIPP: Preterm infant pain profile**, N-PASS:** Neonatal pain agitation and sedation scale**, INFANIB:** Infant neurological international battery**, TIMP:** Test of infant motor performance**, MCID:** Minimal clinically important difference

3.8. Materials to be used: Stationeries, Internet, Computer, Mobile phones

3.9. Procedure:

3.9.1. Ethical statement

The study was approved by Research Advisory Committee (RAC) of MMIPR on 10th August, 2021, Mullana, and Haryana. Ethical clearance was obtained from Institutional research ethics committee of Maharishi Markandeshwar Institute of Medical Sciences and Research (MMDU/IEC/2152) on October 13, 2021, and registered in clinicalTrials.gov with unique reference number NCT04366102[62] on 28th April, 2020, and also with Universal trial number (UTN) U1111-1242-9663.The study will be performed according to the National ethical guidelines for biomedical and health research involving human participants (Indian council of medical research, 2017) And Helsinki declaration (Revised, 2013).

3.9.2. Recruitment and allocation

Preterm neonates experiencing procedural pain will be recruited via caregiver/parental consent from recognized tertiary care teaching hospital for this multi arm pretest postest trial.

3.9.3. Sample size

Sample size estimation was performed with G* Power software version 3.1.9.4. by using two statistical test, Wilcoxon Signed-rank test (matched pairs), and Wilcoxon-Mann-Whitney test (two groups). Sample size was calculated as a priori, by considering 0.81 as effect size, a required sample size of n=15 for matched pairs and n=54 (27 in each

group) for two groups were obtained, at 5% alpha error and 80% power of the study. Thus, considering a 20 % drop out rate in each group, the minimal required sample size was estimated to be, n=18 (matched pairs) and n=66 (two groups; n=33/group). When considering the above both statistical tests, we will recruit the higher sample size, n=66 in this study to satisfy both the conditions.

Figure 3.1: Sample size estimation for matched pairs

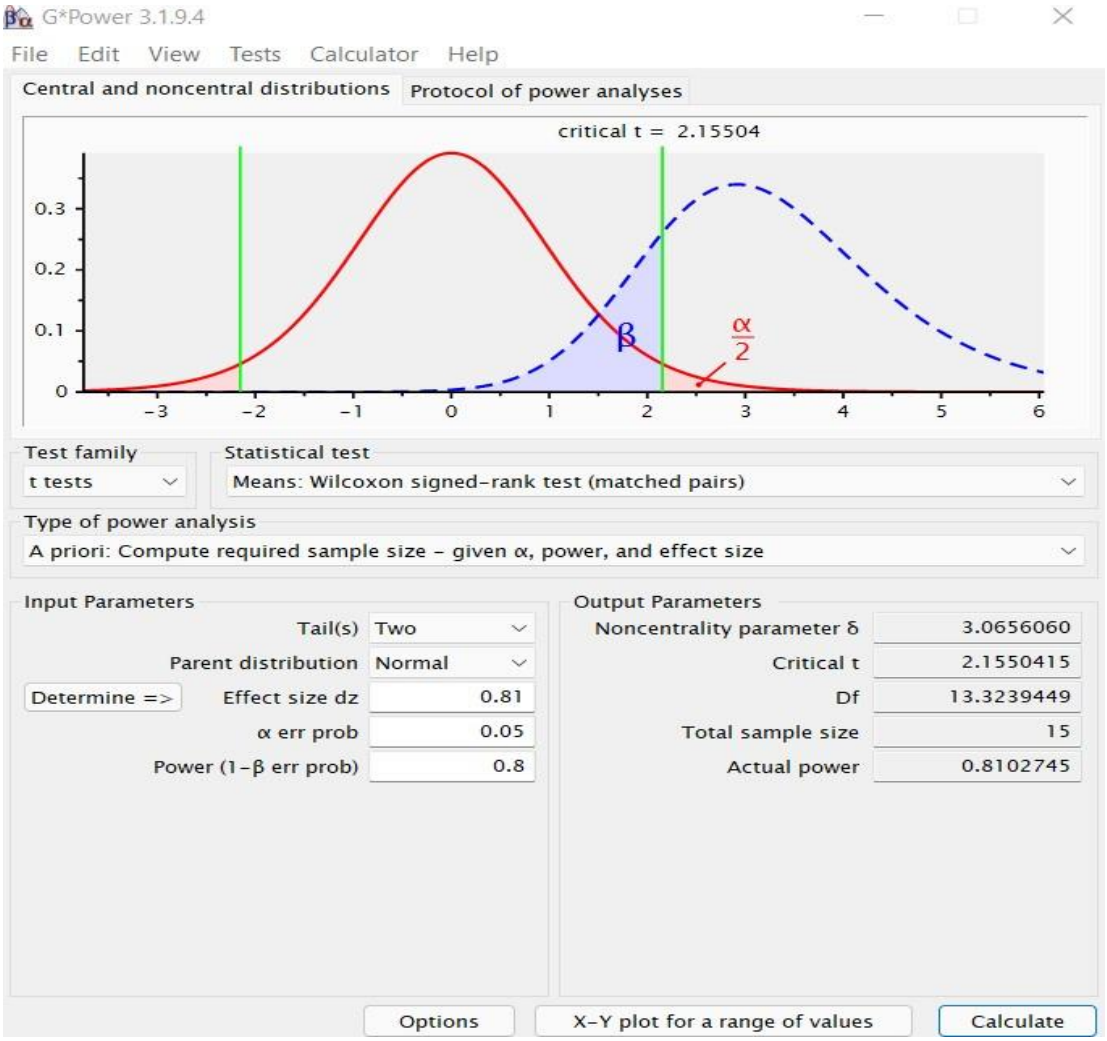
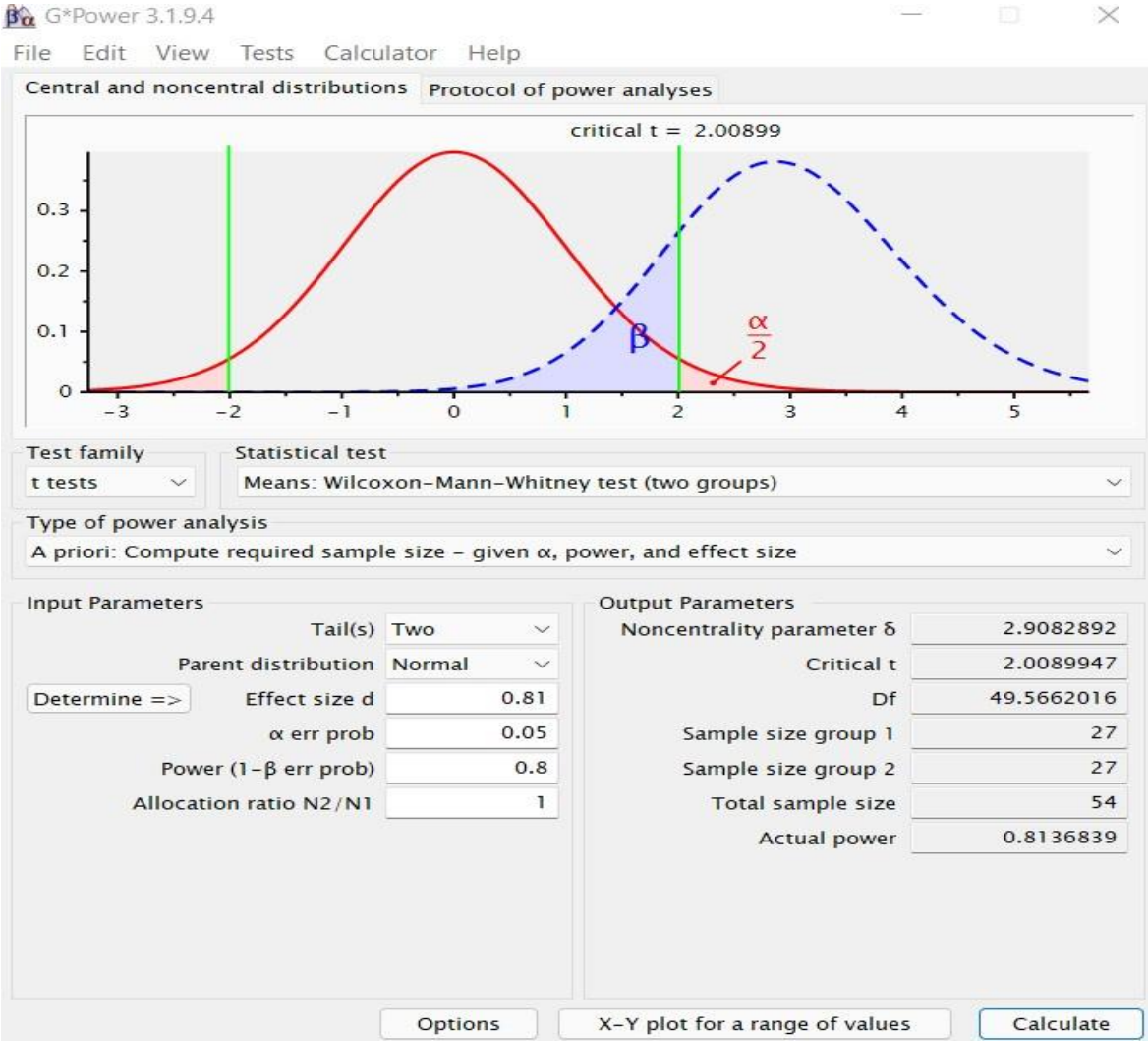


Figure 3.2: Sample size estimation for two groups

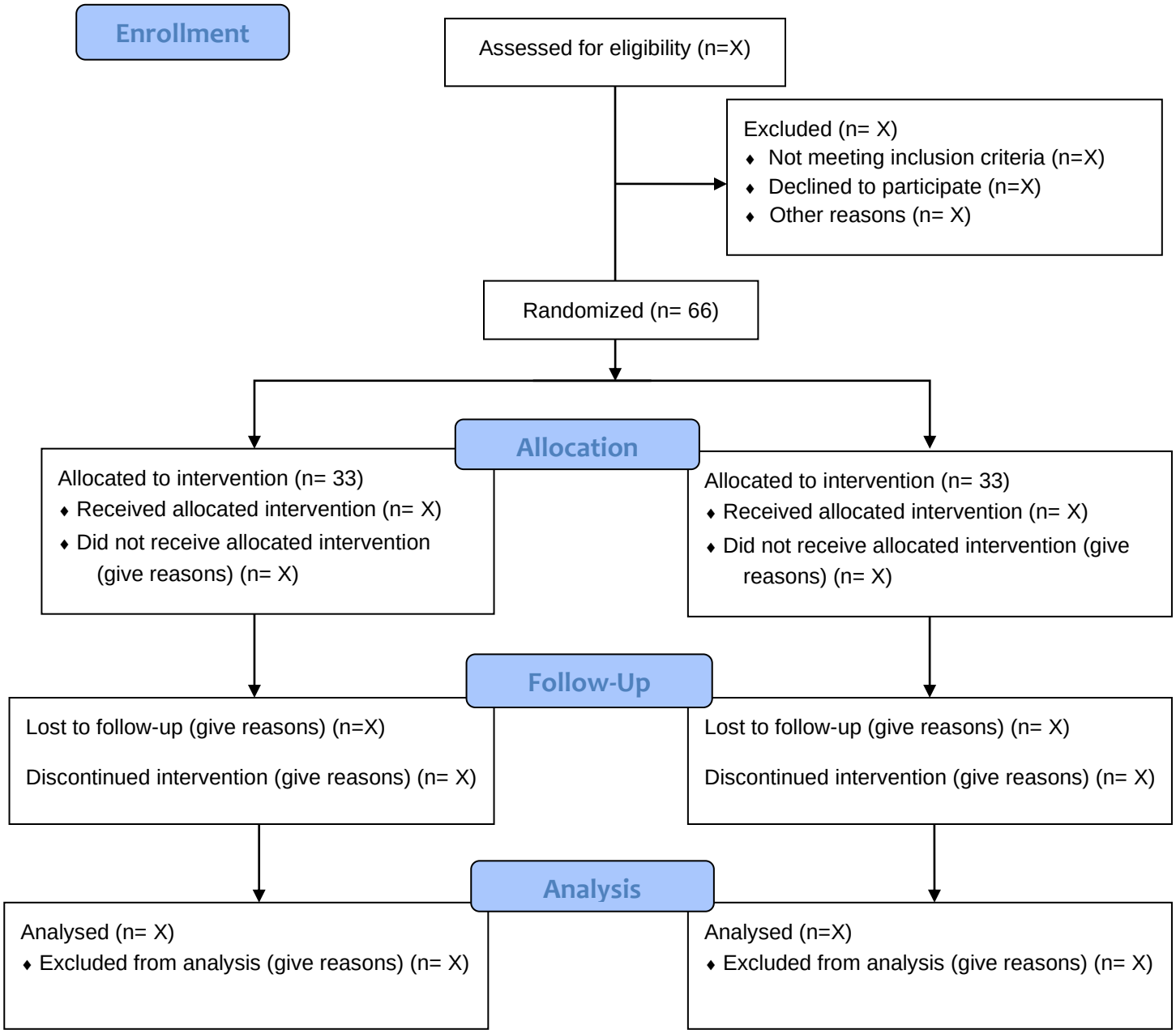


3.9.4. Randomization and blinding

The study will follow randomized consent randomization. The randomization scheme will be based on a block randomization procedure, and participants will be allocated to either an experimental or a comparator group. As we obtained total sample size of 66 according to it, there will be four blocks with matrix design of 4 X 17 where seventeen being rows. Allocation concealment will be done by Sequentially Numbered Opaque

Sealed Envelopes (SNOSE). The subjects will be allocated to one of the treatment groups based on the randomly chosen envelope SNOSE by blinded neonatal nurses. It will follow randomized consent randomization. Staff involved in the study will be blinded at the point of randomization to prevent allocation bias.

3.3. Figure: Flowchart of participant inclusion


Enrollment
Assessed for eligibility (n=X)
Excluded (n= X)
♦ Not meeting inclusion criteria (n=X)
♦ Declined to participate (n=X)
♦ Other reasons (n= X)
Randomized (n= 66)
Allocation
Allocated to intervention (n= 33)
♦ Received allocated intervention (n= X)
♦ Did not receive allocated intervention (give reasons) (n= X)
Allocated to intervention (n= 33)
♦ Received allocated intervention (n= X)
♦ Did not receive allocated intervention (give reasons) (n= X)
Follow-Up
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (n= X)
Lost to follow-up (give reasons) (n= X)
Discontinued intervention (give reasons) (n= X)
Analysis
Analysed (n= X)
♦ Excluded from analysis (give reasons) (n= X)
Analysed (n=X)
♦ Excluded from analysis (give reasons) (n= X)

3.11. Intervention details

Total 30 minutes of treatment plan consists of MSS and Soft tissue therapy will be given to the preterm neonates after 24 hrs. of birth to 5 days of NICU stay.[36] Group A will receive combined MSS and soft tissue therapy for 5 consecutive days of NICU Stay. Group B will receive Routine NICU Care.[63]

Multisensory stimulation	**Soft tissue therapy**
Olfactive stimulation (3 min): Sterile gauzes wet in 2ml of vanilla essence will be placed 10cm away from neonatal nostrils **Vestibular stimulation (3 min):** Gentle horizontal and vertical rocking **Tacto-Kinesthetic stimulation (3 min):** Gentle range of motion of upper and lower limbs **Visual stimulation (3 min):** Black and white stimulation card hung at a distance of 20-25 cm **Oral stimulation (3 min):** Gentle stroking of cheeks, lips, jaw, tongue, and gums	**Forehead and face (3 min):** • Stroking X 30 sec (6 moves: *From forehead towards chin*) • Fingertip Kneading X 1 min. (4 moves: *From forehead towards chin*) • Tapping X 1min. (10 moves: *in synchronized sequence of middle and index fingers*) • Effleurage X 30sec (6 move: *Chin to External auditory meatus, then from forehead to External auditory meatus*) • In the sequence: Forehead-Cheeks-Tapping-followed by Effleurage, and Vice- Versa **Back and Neck (3 min):** • Stroking X 30 sec (6 moves: *In Cephalo-Caudal direction*) • Flat finger kneading X 1min. 12 moves (6 moves per side: *8 O'*

	Clock-11 O' Clock- Right hand, 4 O' Clock- 1 O' Clock- Left hand) • Skin rolling X 1 min. (*Medial to lateral or Spine to Periphery*) • Effleurage X 30 sec (6 moves*: In Caudal-Cephalic direction*) **Chest and abdomen (3 min.):** • Stroking X 30 sec (6 moves: *Upper border of clavicle towards Anterior superior iliac spine*) • Flat finger kneading X 1 min: 12 moves (6 moves per side: *8 O' Clock-11 O' Clock- Right hand, 4 O' Clock- 1 O' Clock- Left hand*) • Skin rolling X 1min. (each side 30 sec : 6 moves per side from ASIS towards upper border of clavicle, Center to periphery) • Effleurage X 30 sec (6 moves: In Caudal-Cephalic direction) **Upper limbs (3 min)** • Stroking X 30 sec (6 moves: *from shoulder towards wrist*) • Transverse friction X 1min. (*Elbow and shoulder joint line*) X (30 sec each side) • Hacking X 1 min. (30 sec each side from fingers: *Distal to proximal from wrist to shoulder*) • Effleurage: 30 sec (6 moves: *Distal*

	to proximal from wrist to shoulder) **Lower Limbs (3 min):** • Stroking X 30 sec (6 moves: *from thigh downwards ankle*) • Transverse friction X 1min. (*Knee and ankle-subtalar joint line*) X (30 sec each side) • Hacking X 1 min. (30 sec each side from fingers: *Distal to proximal from ankle towards thigh*) • Effleurage: 30 sec (6 moves: *Distal to proximal from ankle towards thigh*)
For 15 minutes	**For 15 minutes**

Figure 3.4: Flowchart of allocation, intervention and outcomes details

	Enrolment	**Allocation**	**Post-allocation**				**Close-out**
TIMEPOINT**	t_1	t_1	t_1	t_2	t_3	t_4	t_5
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
[List other procedures]							
Allocation		X					
INTERVENTIONS:							
[Multisensory stimulation and Soft tissue therapy]			X				X
[Routine NICU Care]			X				X
ASSESSMENTS:							
[Premature infant pain profile-Revised (PIPP-R)]			X				X
[Neonatal pain, sedation scale (N-PASS)]			X				X
[Infant Neurological International Battery (INFANIB)]			X				X
Premie Neuro			X				X

3.11. Statistical analysis

The collected demographic and outcome measures will be assessed for their normality using Kolmogorov Smirnov test. If the data follow normal distribution, it will be expressed in descriptive statistics. Repeated measures ANOVA/ Friedman test will be adopted based on normal distribution, to find out the differences within the group at 5 stages (immediately after painful procedure, at 30s, 60s, 90s, and 120s). Independent t test/ Kruskal Wallis test will be adopted based on normal distribution, to find out the differences between the groups at 5 stages (immediately after painful procedure, at 30s, 60s, 90s, and 120s). Paired t test/ Wilcoxon sign ranked test will be adopted based on normal distribution, to find out the differences within Group-A, and Group-B for pre-post intervention changes for neurodevelopmental outcomes. Independent t test/ Mann-Whitney t test will be used based on normal distribution, to compare the changes in mean values of the outcome measures between Group-A, and Group- B at baseline and end of 5 days of intervention for neurodevelopmental outcomes. All the data will be analyzed using statistical software, statistical package for social science (SPSS), IBM SPSS version 20.0 (Armonk, NY: IBM Corp.). The p-value ≤0.05 will be considered to be statistically significant.

4. Discussion

Preterm neonates undergo many repetitive painful procedures as part of their standard care when admitted in NICU. Repeated painful stimuli May have negative on impact neonatal physical and neuro-behavioral development. Despite, the use of a various non-pharmacological interventions, neonatal pain is still remains a concern for neuromotor development.[20] Researchers are focusing on many new non-pharmacological interventions to target repetitive procedural pain among neonates.[16,23,64] Non-pharmacological interventions are one of the promising solution for relieving pain and neurodevelopment outcomes in neonates.[39]

In 2006, the American Academy of Pediatrics and the Canadian Pediatric Association published a policy stating that every health care facility should establish a neonatal pain management program that assesses frequent episodes of routine pain, reducing the risk of painful interventions and reducing and preventing acute attacks. Neonatal pain is best controlled using a multi-pronged approach that includes non-pharmacological and pharmacological modalities. Pain associated with procedures; they are not as effective as when used in combination with other non-pharmacological therapies. Glucose or sucrose, when used in conjunction with a non-nutritious diet, reduces infant pain.

MSS used in conjunction with oral intake or sucrose has been shown to further reduce pain associated with minor pain procedures. For example, this would include placing a sweet solution on the infant's tongue, then gently massaging the face while calmly talking to the infant. However, when used in combination with sweet solutions, sucrose is less effective than sweet solutions. Breastfeeding in combination with the administration of glucose or sucrose has also shown reduced pain compared to

individuals. Skin-to-skin exposure when used with glucose or sucrose reduces pain in infants associated with minor procedures than when used alone. MSS and another analgesia, involves multistage stimulation, including tactile, tactile, auditory and visual stimuli. Sensor saturation used in conjunction with oral intake or sucrose has been shown to further reduce pain associated with mildly painful procedures, and a suitable method for obtaining optimal pain relief.

Previous studies, combined non-pharmacological interventions are found to be more effective than single non-pharmacological interventions.[36] They are safe for treating repetitive procedural pain among preterm neonates. However, studies assessing the combined effects of non-pharmacological interventions are lacking. MSS is more effective in reducing pain than unimodal or single non-pharmacological intervention (Oral sucrose) reported by the previous study.[39] MSS given in combination with other non-pharmacological intervention (oral glucose), potentiates its analgesic effects, and relive pain among neonates.

Previous studies also reported the beneficial effects of MSS on behavioral states and neuromotor development in preterm neonates.[39] Studies[44,65] also reported that massage therapy helps in reducing procedural analgesia in neonates admitted in NICU. Therefore, this trial addresses the need for checking combined effects of MSS with soft tissue therapy in relieving repetitive procedural pain among preterm neonates.

4.1. Strength of the study

4.1.1. Sample size calculated as a priori

4.1.2. Transparency in documenting the outcome, as video will be recorded

4.2. Limitations of the study

4.2.1. Single center study

4.2.2. Blinding is not possible as it is a part of academic research

4.3. Clinical implication

4.3.1. This study will provide the standardized physiotherapy protocol for preterm neonates undergoing painful procedures

5. References

1. Ranger M, Grunau RE. Early repetitive pain in preterm infants in relation to the developing brain. Pain Manag. 2014;4(1):57–67.

2. Walker SM. Neonatal pain. Paediatr Anaesth. 2014;24(1):39–48.

3. Campbell-yeo M, Fernandes A. Procedural Pain Management for Neonates Using Nonpharmacological. Found newborn care. 2011;11(5):312–8.

4. De Clifford Faugere G, Lavallee A, Aita M. Olactive stimulation interventions for managing procedural pain in preterm and full-term neonates: a systematic review protocol. Biomed Cent. 2017;203:1–6.

5. Elisa Palma I, Fernanda Von Wussow K, Ignacia Morales B, Javier Cifuentes R, Sergio Ambiado T. Stress in parents of newborns hospitalized in a Neonatal Intensive Care Unit. Rev chil pedaitr. 2017;88(3):332–9.

6. Claudia A, Prestes Y, Cássia R De, Balda X, Mara G, Maria L, et al. Painful procedures and analgesia in the NICU : what has changed in the medical perception and practice in a ten-year period ? J Pediatr (Rio J). 2016;92(1):88–95.

7. Carbajal R, Rousset A, Danan C, Saizou C. Epidemiology and Treatment of Painful Procedures in Neonates in Intensive Care Units. JAMA. 2008;300(1):60–70.

8. Carter BS, Brunkhorst J. Neonatal pain management. Semin Perinatol [Internet]. 2017;41(2):111–6. Available from: http://dx.doi.org/10.1053/j.semperi.2016.11.001

9. Williams MD, Lascelles BDX. Early Neonatal pain- A review of clinical and experimental implications on painful conditions later in life. Front Pediatr. 2020;8(2):1–18.

10. Puchalski M, Hummel P. The reality of neonatal pain. Adv neonatal care. 2002;2(5):233–47.

11. Hall RW, Anand K. Short and Long-term Impact of Neonatal Pain and stress: More than an Ouchie. Neoreviews. 2009;6(2):69–74.

12. Hall RW. Pain Management in Newborns. Clin Perinatol. 2014;41(4):895–924.

13. Anand KJS. Pharmacological approaches to the management of pain in the neonatal intensive care unit. J Perinatol. 2007;27:4–11.

14. Mangat AK, Oei J lee, Chen K, Quah-smith I, Schmölzer GM. A Review of Non-Pharmacological Treatments for Pain Management in Newborn Infants. Child. 2018;5(10):1–12.

15. Hall RW, Anand KJS. Pain managment in newborns. Clin Perinatol. 2014;41(4):895–924.

16. Bucsea O, Pillai Riddell R. Non-pharmacological pain management in the neonatal intensive care unit: Managing neonatal pain without drugs. Semin Fetal Neonatal Med. 2019 Aug;24(4):10–7.

17. Mohamed EK, Abdelazeim F, Elshafey MA. Neurobehavioral response to multisensory stimulation programme in high-risk neonates. Bull Fac Phys Ther. 2018;23(1):22–9.

18. Bellieni CV, Bagnoli F, Perrone S, Nenci A, Cordelli DM, Fusi M, et al. Effect of Multisensory Stimulation on Analgesia in Term Neonates : A Randomized Controlled Trial. Pediatr Res. 2002;51(4):460–3.

19. Massaro AN, Hammad TA, Jazzo B, Aly H. Massage with kinesthetic stimulation improves weight gain in preterm infants. J Perinatol [Internet]. 2009;29(5):352–7. Available from: http://www.nature.com/doifinder/10.1038/jp.2008.230

20. American Academy of pediatrics. Prevention and Management of Pain in the Neonate : An Update. Pediatrics. 2006;118(5):2231–41.

21. Midmer DK. Pain Perception in the Neonate : A Matter of Opinion. Can Fam Physician. 1989;35:1049–54.

22. Perry M, Tan Z, Chen J, Weidig T, Xu W, Cong XS. Neonatal Pain: Perceptions and Current Practice. Crit Care Nurs Clin North Am. 2018 Dec;30(4):549–61.

23. Golianu B, Krane E, Seybold J, Almgren C, Anand KJS. Non-Pharmacological Techniques for Pain Management in Neonates. Semin Fetal Neonatal Med [Internet]. 2007;31(5):318–22. Available from: http://dx.doi.org/10.1053/j.semperi.2007.07.007

24. Allegaert K, Tibboel D. Neonatal pain management: Still in search for the Holy Grail. Int J Clin Pharmacol Ther. 2016;18(1):42–7.

25. Anand H. Pain Management in Newborn [Internet]. Vol. 41, Clin Perinatol. 2015. 895–924 p. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254489/pdf/nihms626365.pdf

26. Nimbalkar SM, Chaudhary NS, Gadhavi K V, Phatak A. Kangaroo mother care in reducing pain in preterm neonates on heel prick. Indian J Pediatr. 2013;80(1):6–10.

27. Ludington-Hoe SM, Hosseini RB. Skin-to-Skin contact analgesia for preterm infantt heel stick. AACN Clin Issues. 2005;16(3):373–87.

28. Kucukoglu S, Kurt S, Aytekin A. The effect of the facilitated tucking position in reducing vaccination-induced pain in newborns. Ital J Pediatr [Internet]. 2015;41:1–7. Available from: http://dx.doi.org/10.1186/s13052-015-0168-9

29. Cignacco E., Sellam G, Stoffel Li, Gerull R. Oral sucrose and "'Facilitated tucking'" for repeated pain relief in preterms: A randoized controlled trail. Pediatrics. 2012;129(2):1–10.

30. Suhrabi Z, Taghinehad H, Valian K, Sayehmiri K, Taheri S. A comparative study on efficacy of glucose and sucrose on the vaccination pain: A Randomized Controlled Clinical Trial. J Clin Diagnostic Res. 2014;8(10):1–3.

31. Vu-Hgoc H, Cao Minh Uyen H, Phuc Thinh O. Analgesic effect of non-nutritive sucking in term neonates: A randomized controlled trail. Pediatr Neonatol. 2020;61(1):106–13.

32. Shabani F, Dehghan N, Karimi R, Zarei K, Chehrazi M. Effects of music therapy on pain response induced by blood sampling in premature infants: A randomized cross-over trial. Iran J Nurs Midwifery Res. 2016;21(4):391–6.

33. Jain A, Upadhyay K, Lakhkar B. Music Therapy in Neonates for Procedural Pain.

J Datta Meghe Inst Med Sci Univ. 2020;14(2):83–6.

34. El Did M, Massaro AN, Glass P, Aly H. Neurodevelopment assessment of the newborn: An opportunity for prediction of outcomes. Brain Dev. 2011;23:95–105.

35. Zeraati H, Shahinfar J, Vashani HB, Reyhani T. Effect of Multisensory Stimulation on Pain of Eye Examination in Preterm Infants. Anesth pain Manag. 2017;7(1):1–7.

36. Kanagasabai PS, Mohan D. Effect of Multisensory Stimulation on Neuromotor Development in Preterm Infants. Indian J Pediatr. 2013;80(6):460–4.

37. Owens ME, Todt EH. Pain in infancy: neonatal reaction to a heel lance. Pain. 1984 Sep;20(1):77–86.

38. Bellieni CV, Bagnoli F. Effect of multisensory stimulation on analgesia in term neonates: a randomized controlled trail. Pediatr Res. 2002;51:460–3.

39. Yuyun S, Fitri R, Lusmilasari L, Juffrie M, Bellieni CV. Modified Sensory Stimulation Using Breastmilk for Reducing Pain Intensity in Neonates in Indonesia : A Randomized Controlled Trial. J Pediatr Nurs. 2020;53:199–203.

40. Sharma N, Aranha VP, Saxena S, Ateef M, Samuel AJ. Scoping out the scope of scoping reviews in neonatal and pediatric pain management: A scoping review methodological framework. J Pediatr Surg. 2021;

41. Zeerati H, Nasimi F, Zade Ghorban M. Effect of Multi-sensory stimulation on neuromuscular development of premature infants: A randomized clinical trial. Iran J Child Neurol. 2018;12(3):32–9.

42. Field TM, Schanberg SM, Scafidi F, Bauer CR, Vega-Lahr N, Garcia R, et al. Tactile/Kinesthetic Stimulation Effects on Preterm Neonates. Pediatrics. 1986;77(5):654–8.

43. Alvarez MJ, Fernandez-Garcia D, Gomez-Salgado J, Ordas B, Rodriguez-Gonzalez MD, Martinez-Isasi S. Effectiveness of the application of massage therapy and kinesitherapy by parents on premature neonates: A research protocol. J Adv Nurs. 2019 Jun;75(11):3097–104.

44. Yuyun S, Fitri R, Khadijah S, Nurhidayah I. Massage therapy as a non-pharmacological analgesia for procedural pain in neonates : A scoping review. Complement Ther Med. 2021;59:1–8.

45. Ibrahim EM, El-guindy SR, Rashad M. Effect of foot massage on pain responses to heel stick in preterm infants. Med J Cairo Univ. 2016;82(2):25–31.

46. Zargham-Boroujeni, Elsagh A, Mohammadizadeh M. The Effect of Massage and Breastfeeding on response to venipuncture pain among hospitalized neonates. Iran J Nurs Midwifery Res. 2017;22(4):308–12.

47. Bayomi OR, El-Nagger NS. Effect of appying massage therapy on physical, physiological and behavvioral states of premature neonates. J Nurs Educ Pract. 2015;5(10):105–14.

48. Wilson-smith EM. Procedural pain management in neonates , infants and children. Rev pain. 2011;5(3):4–12.

49. Ecevit A, Ince DA, Tarcan A, Cabioglu MT, Kurt A. Clinical Observations

Acupuncture in Preterm Babies during Minor Painful Procedures. J Tradit Chinese Med [Internet]. 2011;31(4):308–10. Available from: http://dx.doi.org/10.1016/S0254-6272(12)60009-0

50. Johnston CC, Filion F, Campbell-yeo M, Goulet C, Bell L, Mcnaughton K, et al. Kangaroo mother care diminishes pain from heel lance in very preterm neonates : A crossover trial. BMC Pediatr. 2008;9:1–9.

51. Unanue R, Westcitt S. Responsiveness of the Test of Infant Motor Performance (TIMP) in infants born Preterm. Pediatr Phys Ther. 2005;17:219–24.

52. Constantinou J. Neurobehavioral assessment predicts differential outcome between VLBW and ELBW preterm infants. J Perinatol. 2005;25:788–93.

53. Provenzi L, Olson K, Giusti L, Montirosso R, Desantis A, Tronick E. NICU Network Neurobehavioral Scale: I-month normative data and variation from birth to 1 month. Pediatr Res. 2018;83:1104–9.

54. Donna K. Daily, Canon S, Pineda RG. The Premie-Neuro. 3rd ed. USA; 2019. 1–32 p.

55. Fernandez D, Alvarez MJ, Rodriguez D, Rodriguez M. Spanish Validation of the Premie-Neuro Scale in Premature Infants. J Pediatr Nurs. 2015;30(4):560–7.

56. Allinson LG, Denehy L, Doyle LW, Eeles AL. Physiological stress responses in infants at 29-3 weeks postmenstrual age during clustered nursing cares and standardised neurobehavioral assessments. BMJ Pediatr Open. 2017;(1):1–8.

57. George JM, Fiori S, Fripp J, Pannek K, Guzzetta A. Relationship between very

early brain structure and neuromotor, neurological and neurobehavioral function in infants born <31 weeks gestational age. Early Hum Dev. 2018;117:74–82.

58. George JM, Colditz PB. Early clinical and MRI biomarkers of cognitive and motor outcomes in very preterm born infants. Pediatr Res. 2021;

59. Pineda RG, Liszka L, Terrie. Early Neurobehavior at 30 weeks postmenstrual age is related to outcome at term equivalent age. Early Hum Dev. 2020;146(7):1–13.

60. Hummel P, Puchalski M, Weiss MG. Clinical reliability and validity of the N-PASS : neonatal pain , agitation and sedation scale with prolonged pain. J Perinatol. 2008;28(1):55–60.

61. Kanagasabai PS, Mohan D. Effect of Multisensory Stimulation on Neuromotor Development in Preterm Effect of Multisensory Stimulation on Neuromotor Development in Preterm Infants. 2013;(January).

62. ClinicalTrials.gov PRS: Record Summary NCT04366102 [Internet]. [cited 2022 Jul 23]. Available from: https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009TJD&selectaction=Edit&uid=U0002I76&ts=2&cx=igy75f

63. Sharma N, Samuel AJ. Multisensory Stimulation and Soft Tissue Therapy on Pain and Neurodevelopment Among Preterm Neonates. Pediatr Phys Ther [Internet]. 2022 Apr;34(2):277–82. Available from: https://journals.lww.com/10.1097/PEP.0000000000000887

64. Hsieh K hsian, Chen S jen, Tsao P chen, Wang C chien, Huang C feng, Lin C

ming, et al. The analgesic effect of non-pharmacological interventions to reduce procedural pain in preterm neonates. Pediatr Neonatol [Internet]. 2018;59(1):71–6. Available from: https://doi.org/10.1016/j.pedneo.2017.02.001

65. Aly F, Murtaza G. Massage Therapy in Preterm Infants. Pediatr Ther. 2013;3(2):2–4.

Annexure 1

INSTITUTIONAL ETHICAL COMMITTEE

MAHARISHI MARKANDESHWAR INSTITUTE OF MEDICAL SCIENCES & RESEARCH MULLANA, AMBALA

Communication of Decision of the Ethics Committee (IEC)

Project No: IEC- 9152

Project Title: Multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopment among preterm neonates
Name of Student/Scholar: Neha Sharma
Name of Institution: MMIPR, MULLANA (AMBALA)
☑ New review ☐ Revised review ☐ Expedited review
Date of review (D/M/Y): 13-10-2021 Date of previous review, if revised application: ----------
Decision of the Ethics Committee: ☑ Recommended ☐ Recommended with suggestions ☐ Revision ☐ Rejected
Remarks: Approved
Recommended for a period of : 1 year

Please note *

- **Inform EC immediately in case of any adverse events and serious adverse events.**
- **Inform EC in case of any change of study procedure, site and investigator**
- **This permission is only for period mentioned above. Annual report to be submitted to EC.**
- **Members of EC have right to monitor the trial with prior intimation.**

Signature of Member Secretary
Ethics Committee
MMIMSR

Annexure 2

Data assessment sheet

Code: Group:

Date of birth:

Date of assessment: GA at birth: APGAR score:

at 1 min: 5 min: 10 min:

Birth weight: AGA/SGA/LGA:

Length of NICU stay:

Particulars	D1OA	D2OA	D3OA	D4OA	D5OA
Corrected GA					
State related behavior					

Anthropometrics:

Weight					
Crown heel length					
OFC					

Pain assessment Underwent Procedure:

Outcome measures	D1OA				D5OA			
	At 30s	60s	90s	120s	At 30s	60s	90s	120s
PIPP-R								
N-PASS								

Neuromotor assessment

Outcome measures	D1OA	D5OA
INFANIB		
Premie Neuro		

GA: Gestational age; DOA: Day of assessment; OFC: Occipital Frontal Circumference; BMI: Body Mass Index; PIPP-R: Preterm Infant Pain Profile-Revised, N-PASS: Neonatal Pain agitation sedation scale, INFANIB: Infant Neurological International Battery

Annexure 3

Consent Form (English)

This information consent form is for parents, whom newborns are admitted in Neonatal intensive care units (NICU).

Name of Principal investigator: Mrs. Neha Sharma, MPT

Name of organization: Maharishi Markandeshwar Institute of Physiotherapy and rehabilitation, Maharishi Markandeshwar (Deemed to be university), Mullana, Ambala, Haryana, India

Name of supervisor: Prof. **(**Dr.) Asir John Samuel, PhD

Name of sponsor: DST/INSPIRE (Innovation in science pursuit for Inspired Research) Fellowship [IF190481], Government of India.

Name of Proposal: Multisensory stimulation and soft tissue therapy on procedural pain and neurodevelopment among preterm neonates

This informed consent is having two parts:

- Information sheet
- Certificate of consent

Part 1: Information sheet

Introduction: I am Neha Sharma pursuing Doctorate of Philosophy in Physiotherapy under supervision of Dr. Asir John Samuel. I am doing research on combined effects of movement and massage therapy given along with visual stimulation cards, vanilla essence for smell stimulation, oral stimulation with finger, and horizontal and vertical rocking in managing procedural pain and improving brain

growth and development in newborns undergoing repetitive painful procedures. Combined effects of these interventions can improve procedural pain and brain growth development in newborns. In this trail, I am going to perform combination of movement and massage therapy along with different sensory stimulations.

Purpose: Repetitive painful procedure among newborns causes abnormal brain growth and development during NICU stay. The purpose of this research is to determine the effects of movement and massage therapy along with different sensory stimulations in improving pain and promoting brain growth development among newborns.

Type of research intervention: Combination of movement and massage therapy along with different sensory stimulations will be given to the newborns.

Participant selection: The trial will be performed on newborns undergoing repetitive painful procedures, to provide immediate pain relief and promote brain growth and development during NICU stay.

Voluntary participation: Your newborn doesn’t have to be in this research if you don't want to be. It’s up to you. If you decide not to be in the research, it is okay and nothing changes. Even if you say "yes" now, you can change your mind later and it’s still okay.

Procedures and Protocol: In this trial, I am going to see the combined effects of movement and massage therapy given along with visual stimulation cards, vanilla essence for smell stimulation, oral stimulation with finger, and horizontal and vertical rocking in managing procedural pain and improving brain growth and development in newborns undergoing repetitive painful procedures. I am going to see that if this trial will helps newborns to provide immediate pain relief and promotes brain growth and development or not.

Movement and massage therapy with different stimulations will be given once a day for 5 days of NICU Stay.

This exercise regimen did not harm your newborn and have no such side effects. If you will not feeling comfortable with the procedure, then your newborn will be withdrawn from the study any time.

A. Unfamiliar Procedures

Because we do not know if the new intervention is better than routine NICU care for relieving pain and promoting brain growth and development, we need to make comparisons. Newborns taking part in this research will be put into groups which are selected by chance through chit method. One group will get the Movement and massage therapy with different sensory stimulations we are testing, and the other group will get the Routine NICU Care. It is important that neither you nor we know among which of them your child was given. This information will be in our files, but we will not look at these files until after the research is finished. We will then compare which of the two has the best results.

B. Description of the Process

Your newborn will receive the treatment for his/her condition according to guidelines by American Academy of Pediatrics. Movement and massage therapy given along with visual stimulation cards, vanilla essence for smell stimulation, oral stimulation with finger, and horizontal and vertical rocking will only given. No blood sampling procedures will be performed by principal investigator in this trial.

Duration: Intervention will be given for 30 minutes per day, for 5 days of NICU Stay

Side effects: These interventions do not have any side effects. However, we will follow your newborn closely and keep track of any other associated problems.

Risks: Both the interventions are safe, and no risks are associated with the interventions

Discomforts: By participating in this research it is possible that your newborn may experience some discomfort such as skin redness. This should disappear in one day, but if you are concerned, please call me or come to pediatric physiotherapy OPD/Lab.

Benefits: This intervention program might help in relieving pain and improving neurodevelopment among newborns undergoing repetitive painful procedures

Reimbursements: Any kind of payment will not be provided for taking part in the research.

Confidentiality: The trial will be conducted in NICU. Information about participant inclusion will be confidential and not be shared with anyone.

Sharing the results: Obtained information from the trial will be shared with parents and NICU staff. Result information will also publish in the journal also. However, identity concealment will not be guaranteed. Recorded videos and photographs will be shared in the journal, Scientific conferences, Departmental presentations, Ph.D. thesis, etc. for non-commercial educational purposes.

Right to Refuse or Withdraw: Your newborn does not have to be in this research. No one will be mad or disappointed with you if you say no. It's your choice. You can think about it and tell us later if you want.

Who to contact: If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: email: neha.shar1894@gmail.com, contact: +917018007012

Part 2: Certificate of consent

I am inviting your newborn to take participate in this research trial related to the effects of movement and massage therapy given along with visual stimulation cards, vanilla essence for smell stimulation, oral stimulation with finger, and horizontal and vertical rocking in managing procedural pain and improving brain growth and development in newborns undergoing repetitive painful procedures.

Name of participant_____

Parental signatures_____

Date _____Day/month/Year

If Illiterate:

Thumb print of participant

Statement by the researcher taking consent

I confirm that the parents of the newborns have given opportunity to ask questions about the study, and all the questions asked by parents of the newborns have been answered correctly. I confirm that consent has been given freely and voluntarily.

Name of researcher taking the consent_____

Signature of researcher_____

Date _____Day/month/Year

Annexure 4

Consent Form (Hindi)

यह सूचना सहमति प्रपत्र माता-पिता के लिए है, जिन्हें नवजात शिशु गहन देखभाल इकाइयों (एनआईसीयू) में भर्ती कराया जाता है।

इस सूचित सहमति के दो भाग हैं:

• सूचना पत्रक

• सहमति का प्रमाण पत्र

भाग 1: सूचना पत्र

परिचय: मैं नेहा शर्मा, डॉ. असीर जॉन सैमुअल की देखरेख में फिजियोथेरेपी में डॉक्टरेट ऑफ फिलॉसफी कर रही हूं। मैं प्रक्रियात्मक दर्द के प्रबंधन में बहुसंवेदी उत्तेजना (दृश्य उत्तेजना कार्ड, गंध उत्तेजना के लिए वेनिला एसेंस, उंगली से मौखिक उत्तेजना, और क्षैतिज और ऊर्ध्वाधर रॉकिंग के साथ)

और कोमल ऊतक चिकित्सा के संयुक्त प्रभावों पर शोध कर रही हूं और दोहराए जाने वाले दर्दनाक प्रक्रियाओं से गुजरने वाले नवजात शिशुओं में मस्तिष्क की वृद्धि में सुधार कर रही

हूं। इन हस्तक्षेपों के संयुक्त प्रभाव नवजात शिशुओं में प्रक्रियात्मक दर्द और मस्तिष्क की वृद्धि परिणामों में सुधार कर सकते हैं। इस निशान में, मैं एनआईसीयू प्रवास के दौरान दर्दनाक प्रक्रियाओं से गुजरने वाले नवजात शिशुओं के बीच संवेदी उत्तेजनाओं और कोमल मालिश चिकित्सा करने जा रही हूं।

शोध का उद्देश्य: नवजात शिशुओं में दर्द में सुधार और मस्तिष्क की वृद्धि को बढ़ावा देने में के प्रभावों का निर्धारण करना

अनुसंधान हस्तक्षेप का प्रकार: नवजात शिशुओं को संवेदी उत्तेजनाओं और कोमल मालिश तकनीकों का संयोजन दिया जाएगा।

प्रतिभागियों का चयन: एनआईसीयू में रहने के दौरान तत्काल दर्द से राहत और मस्तिष्क के विकास और विकास को बढ़ावा देने के लिए दोहराए जाने वाले दर्दनाक प्रक्रियाओं से गुजरने वाले नवजात शिशुओं पर परीक्षण किया जाएगा।

स्वैच्छिक भागीदारी: यदि आप नहीं बनना चाहते हैं तो आपके नवजात शिशु को इस शोध में शामिल होने की आवश्यकता नहीं है। यह आप पर निर्भर करता है। यदि आप शोध में शामिल नहीं होने का निर्णय लेते हैं, तो कोई बात नहीं और कुछ भी नहीं बदलता है। यहां तक कि अगर आप अभी "हां" कहते हैं, तो आप बाद में अपना विचार बदल सकते हैं और यह अभी भी ठीक है।

प्रक्रिया: इस परीक्षण में, मैं दृश्य उत्तेजना कार्ड, गंध उत्तेजना के लिए वेनिला एसेंस, उंगली से मौखिक उत्तेजना, और प्रक्रियात्मक दर्द के प्रबंधन और मस्तिष्क के विकास में सुधार के लिए क्षैतिज और ऊर्ध्वाधर रॉकिंग के साथ दिए गए आंदोलन और मालिश चिकित्सा के संयुक्त प्रभावों को देखने जा रहा हूं। और दोहरावदार दर्दनाक प्रक्रियाओं से गुजर रहे समय से पहले के नवजात शिशुओं में विकास। मैं यह देखने जा रहा हूं कि क्या यह परीक्षण नवजात शिशुओं को तत्काल दर्द से राहत दिलाने में मदद करेगा और मस्तिष्क के विकास और विकास को बढ़ावा देगा या नहीं।

एनआईसीयू स्टे के 5 दिनों के लिए विभिन्न उत्तेजनाओं के साथ आंदोलन और मालिश चिकित्सा दिन में एक बार दी जाएगी।

इस व्यायाम आहार ने आपके नवजात शिशु को कोई नुकसान नहीं पहुंचाया है और न ही इसका कोई दुष्प्रभाव है। यदि आप प्रक्रिया में सहज महसूस नहीं कर रहे हैं, तो आपके नवजात शिशु को किसी भी समय अध्ययन से वापस ले लिया जाएगा।

अवधि: 5 दिनों के लिए 30 मिनट के लिए हस्तक्षेप दिया जाएगा।

जोखिम: दोनों हस्तक्षेप सुरक्षित हैं, और हस्तक्षेप से कोई जोखिम जुड़ा नहीं है।

लाभ: यह हस्तक्षेप कार्यक्रम दोहराए जाने वाले दर्दनाक प्रक्रियाओं से गुजरने वाले नवजात शिशुओं में दर्द से राहत और न्यूरोडेवलपमेंट में सुधार करने में मदद करता है।

प्रतिपूर्ति: शोध में भाग लेने के लिए किसी भी प्रकार का भुगतान नहीं किया जाएगा।

गोपनीयता: परीक्षण एनआईसीयू में आयोजित किया जाएगा। प्रतिभागी समावेशन के बारे में जानकारी गोपनीय होगी और इसे किसी के साथ साझा नहीं किया जाएगा।

परिणाम साझा करना: परीक्षण से प्राप्त जानकारी माता-पिता और एनआईसीयू कर्मचारियों के साथ साझा की जाएगी। रिकॉर्ड किए गए वीडियो और तस्वीरें जर्नल, वैज्ञानिक सम्मेलनों, विभागीय प्रस्तुतियों, पीएच.डी. थीसिस, आदि में साझा किए जाएंगे।

मना करने या वापस लेने का अधिकार: इस शोध में आपके नवजात शिशु का होना जरूरी नहीं है। ना कहने पर कोई आपसे नाराज़ या निराश नहीं होगा। यह तुम्हारी पसंद है। आप इसके बारे में सोच सकते हैं और चाहें तो हमें बाद में बता सकते हैं।

भाग 2: सहमति का प्रमाण पत्र

मैं आपके नवजात शिशु को दर्द से राहत और न्यूरोडेवलपमेंटल परिणामों में सुधार करने में मल्टीसेंसरी उत्तेजना और कोमल ऊतक चिकित्सा के प्रभावों से संबंधित इस शोध परीक्षण में भाग लेने के लिए आमंत्रित कर रही हूं।

प्रतिभागी का नाम_____

माता-पिता के हस्ताक्षर_____

दिनांक _____दिन/माह/वर्ष

अगर निरक्षर

प्रतिभागी का अंगूठा प्रिंट

शोधकर्ता द्वारा सहमति लेने का कथन

मैं पुष्टि करती हूं कि नवजात शिशुओं के माता-पिता ने अध्ययन के बारे में प्रश्न पूछने का अवसर दिया है, और नवजात शिशुओं के माता-पिता द्वारा पूछे गए सभी प्रश्नों का सही उत्तर दिया गया है। मैं पुष्टि करती हूं कि सहमति स्वतंत्र रूप से और स्वेच्छा से दी गई है।

सहमति लेने वाले शोधकर्ता का नाम_____

शोधकर्ता के हस्ताक्षर _____

दिनांक _____दिन/माह/वर्ष

Annexure 5

Plagiarism report

Curiginal

Document Information

Analyzed document	Neha_Synopsis.docx (D111662418)
Submitted	8/25/2021 11:34:00 AM
Submitted by	
Submitter email	asirjohnsamuel@mmumullana.org
Similarity	9%
Analysis address	asirjohnsamuel.mmu@analysis.urkund.com

Sources included in the report

W	URL: https://clinicaltrials.gov/ct2/show/NCT04366102 Fetched: 8/25/2021 11:36:00 AM	11
W	URL: https://www.frontiersin.org/articles/513037 Fetched: 8/25/2021 11:36:00 AM	3
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4254489/ Fetched: 8/25/2021 11:36:00 AM	16
W	URL: https://www.researchgate.net/publication/297890006_A_Guide_to_Pain_Assessment_and_Management_in_the_Neonate Fetched: 11/27/2019 1:16:12 PM	3

Annexure 6

Ph.D. Related Publication_1

Journal of Pediatric Surgery 57 (2022) 1599–1608

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg.org

Review Article

Scoping out the scope of scoping reviews in neonatal and pediatric pain management: A scoping review methodological framework

Neha Sharma, MPT[a], Vencita Priyanka Arahna, MPT[a], Shikha Saxena, PhD[b], Mahamed Ateef, PhD[c], Asir John Samuel, PhD[a,*]

[a] Department of Pediatric and Neonatal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana 133207, India
[b] School Based Rehabilitation Services, Physiotherapy Division, Communicare Therapy Inc., Ottawa , Canada
[c] Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Majmaah University, Al Majmaah 11952, Saudi Arabia

ARTICLE INFO

Article history:
Received 10 June 2021
Revised 12 November 2021
Accepted 14 November 2021

Keywords:
Literature
Neonatal
Pediatric
Pain
Standard of care

ABSTRACT

Purpose: This methodological framework was purposed to discuss the considerations for conducting scoping review for neonatal and pediatric pain management (NPPM) from the perspectives of Arksey and O' Malley and Joanna Briggs Institute (JBI) framework. Till now, there is no scoping review or standard methods are available for identifying, prioritizing, or reporting research gaps in the area of NPPM.
Methods and results: Scoping reviews were utilized to map the literature comprehensively across a range of study designs in a particular area. This methodological framework describes the methods used to identify, prioritize, and display research gaps in the area of NPPM. Different methods to determine research gaps have been described in this framework. This scoping review methodological framework also discussed methods for conducting scoping review in two levels with methodological considerations given by Arksey and O'Malley, and JBI Institute. Search terms and search terminologies are described to conduct scoping review effectively for NPPM. Through, this standard scoping review methodological considerations, the general understanding and current advances in NPPM can be widened.
Conclusion: This methodological framework describes the methods for conducting scoping review effectively in the area of NPPM.
Level of evidence: Not applicable.

© 2021 Elsevier Inc. All rights reserved.

1. Introduction

Neonatal and pediatric pain is more than simply a sensory experience [1]. Postoperative and procedural pain experienced by them has both immediate and long term effects on pain reactivity [2]. In neonates, structural components which are important for perceiving pain are already developed around 25th week of pregnancy, but endogenous descending inhibitory pathways are not completely evolved till mid-infancy. 69.6% of neonates experience painful procedures during their NICU Stay [1]. Because of immature neonatal nervous systems, they experience major neuro-developmental consequences. Repeated nociceptive stimuli affect neonatal neurodevelopment in numerous ways. It increases the risks of neurodevelopmental impairments, adverse effects in neonatal brain development, and alteration in somatosensory functions which leads to pain [2]. Pain experienced during early neonatal period may morphs the somatosensory functioning of upcoming cognitive, perceptual, and social milestone's maturation. Children who are very preterm have lessened brain volumes, and the pain experienced during early infancy is accompanied with low cognitive behaviors, including poor intelligence, poor-visual motor functioning, language, and attention deficits. These deficits will carryovers into the adolescence and adulthood [2].

Many neonatal and pediatric pain management strategies use both pharmacological and non-pharmacological pain relieving strategies [3]. Pharmacological pain-relieving strategies (PPRS) consisting of Multi-modal analgesic techniques are derived from four categories of analgesics like Opoids, local anesthetics, Non-steroidal anti-inflammatory drugs, and acetaminophen, which are beneficial for pain relieving among neonates and children [4]. Non pharmacological pain-relieving strategies (NPPRS) also helps in relieving pain [4]. NPPRS helps in reducing opioids intake and their harmful physiological and psychological responses to pain. NPPRS

NPPM, Neonatal and Pediatric pain management; **PPRS**, Pharmacological pain relieving strategies; **NPPRS**, Non-pharmacological pain relieving strategies; **PCC**, Population, concept and context; **JBI**, Joanna Briggs Institute; **NICU**, Neonatal Intensive care units; OSF, Open Science Framework.

* Corresponding author.
E-mail addresses: neha_sharma@mmumullana.org (N. Sharma), vencita.peds@mmumullana.org (V.P. Arahna), SSaxena@communicare.ca (S. Saxena), m.jeelani@mu.edu.sa (M. Ateef), asirjohnsamuel@mmumullana.org (A.J. Samuel).

Annexure 7

Ph.D. Related publication_2

Multisensory Stimulation and Soft Tissue Therapy on Pain and Neurodevelopment Among Preterm Neonates

Neha Sharma, BPT, MPT (Pediatric Disorders);
Asir John Samuel, BPT, MPT (Neuro Sciences and Pediatric Neurology), PhD (Physiotherapy), BSc (Psychology)

Department of Pediatric and Neonatal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana, India.

Downloaded from http://journals.lww.com/pedpt by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 10/03/2022

Purpose: To determine the combined effects of multisensory stimulation (MSS) and soft tissue therapy (STT) in managing procedural pain and promoting neurodevelopment in neonates undergoing repetitive painful procedures during their neonatal intensive care unit (NICU) stay.
Methods: Total of 104 preterm neonates admitted in NICU will be recruited for this trial. The intervention will be given for 5 consecutive days to both the groups. Experimental group will receive both MSS and STT; control group will receive routine NICU care. The premature infant pain profile and Neonatal Pain, Agitation, and Sedation Scale will be used for assessing procedural pain, and Infant Neurological International Battery and Premie-Neuro will be used for assessing neurodevelopmental maturity. Relevant parametric or nonparametric test will be used to analyze the data for all outcomes.
Discussion: This is a study protocol analyzing the combined effects of nonpharmacological interventions (MSS and STT) in preterm neonates. (Pediatr Phys Ther 2022;34:277–282)
Key words: neonates, NICU, pain, procedural, soft tissue therapy

INTRODUCTION AND PURPOSE

Repeated painful procedures are common in neonates who are admitted in neonatal intensive care unit (NICU).[1] Pain in neonates is difficult to assess because of their inability to express their feelings verbally.[2] Neonates admitted to an intensive care unit are exposed to significant repeated painful procedures at the time when the nervous system is developing and sensitive to changes in sensory experience. Painful procedures, often 10 times per day, are a necessary part of intensive care. Neonates underwent an average of 10 to 14 painful procedures in the first 14 days of admission in an intensive care unit.[3] Increased activity of spinal and cortical nociceptive pathways in preterm and term neonates leads to hyperalgesia.[3] Pain in the neonatal period is associated with detrimental effects on future pain response, sensory processing, and neurodevelopmental outcomes.

Neonatal pain causes adverse neurodevelopmental outcomes following a NICU stay, specifically in preterm neonates.[4] Structural deficits identified are periventricular leukomalacia, decreased white matter volume, small corpus callosal areas, decreased cortical and gray matter, and ventricular hypertrophy confirmed by electroencephalography and functional magnetic resonance imaging techniques.[5] Nonpharmacological interventions are valuable strategies that can reduce neonatal pain directly by blocking nociceptive transduction/transmission by the noxious event through endogenous mechanisms located along the spinothalamic tract or by activation of descending inhibitory pathways.[5] Multisensory stimulation (MSS) is more effective in reducing procedural pain than unimodal nonpharmacological interventions confirmed by the studies. Multisensory stimulation given through various different stimulations (tacto-kinesthetic, auditory, visual, vestibular, oral, and olfactive) helps in neurodevelopment, weight gain, and stress levels. Soft tissue therapy (STT) is also acknowledged as a potential interventional approach for managing pain in NICU settings. Soft tissue therapy given with breastfeeding helps in reducing pain during intravenous blood sampling procedures.

0898-5669/110/3402-0277
Pediatric Physical Therapy
Copyright © 2022 Academy of Pediatric Physical Therapy of the American Physical Therapy Association

Correspondence: Asir John Samuel, BPT, MPT, PhD, BSc, Department of Pediatric and Neonatal Physiotherapy, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala 133207, Haryana, India (asirjohnsamuel@mmumullana.org or asirj.samuel@gmail.com).

At the time this article was written Neha Sharma was a doctoral student at the Maharishi Markandeshwar (Deemed to be University).

Grant Support: This study was funded by the Department of Science and Technology (DST), Government of India.

NS contributed to collection of intellectual content, manuscript preparation, and manuscript review. AJS structured the concepts, design, and definition of intellectual content and manuscript review. Both the authors approved the manuscript.

The authors declare no conflicts of interest.

DOI: 10.1097/PEP.0000000000000887

Annexure 8

INFANIB Scale

PRACTICE

INFANIB

Date of Exam _____

NAME _____ CIRCLE ONE Corrected Gestational Age _____

ITEM	START SCORE	MAJOR CHANGE								
1	Birth		**SUPINE** Hands closed/open		Closed		Sometimes Closed		Open	
2	Birth		Scarf sign	Less Than #1	0° to 15° (1)	15° to 45° (2)	45° to 60° (3)	60° to 85° (4)		Past #4
3	Birth		Heel to ear	Over 100°	90° to 100°	60° to 90°	40° to 60°	10° to 40°		Under 10°
4	Birth		Popliteal angle	Under 80°	80° to 90°	90° to 110°	110° to 150°	150° to 170°		Over 170°
5	Birth		Leg abduction	Under 40°	40° to 70°	70° to 100°	100° to 130°	130° to 150°		Over 150°
6	Birth		Dorsiflexion of foot	0° to 10° Foot/Leg	10° to 40° Foot/Leg	40° to 70° Foot/Leg	70° to 80° Foot/Leg	80° to 90° Foot/Leg		
7	Birth	9 mos.	Foot grasp		No Grasp		Barely Grasp		Grasp	
8	Birth	6 mos.	Tonic labyrinthine supine		Absent		Shoulder retraction or some extension of trunk or legs		Shoulder retraction and full leg extension	
9	Birth	6 mos.	Asymmetric tonic neck reflex		Absent		Postures in, can move out		Persistent	
10	Birth		Pull to sitting		Head extended Arms extended		Head up Arms ext.	Head flexed Arms ext.	Head flexed Arms flexed	
11	4 mos.		Body derotative		Present to both sides		Slow or mildly asymmetrical		Absent or markedly asymmetrical	
12	9 mos		Body rotative		Present		Poor		Absent	
13	Birth		**PRONE** All fours	Lifts Head	Head up 45°	Forearms only	Head up 90°	Bears weight on extended arms	Assumes all fours unsteadily	Assumes all fours well	Stands up through Plantigrade
14	Birth	9 mos.	Tonic labyrinthine prone		Absent		With Head Flexion: Shoulder protraction or some flexion of legs		With Head Flexion: Shoulder protraction and arms, hips, or legs under trunk	
15	Birth		**SITTING** Sitting position			L3		L5		
16	6 mos.		Sideways parachute		Present in both arms		Slow or mildly asymmetrical		Absent or markedly asymmetrical	
17	9 mos.		Backwards parachute		Present in both arms		Slow or mildly asymmetrical		Absent or markedly asymmetrical	
18	Birth		**STANDING** Weight bearing	Primitive reflex	No weight bearing		Poor weight bearing Breaks at knees	Unequal weight bearing		
19	3 mos.		Positive support reaction		Feet flat		5 to 30 sec. on toes then drop to feet flat		>30 sec. on toes	
20	7 mos.		**SUSPENDED** Forward parachute		Present		Slow or mildly asymmetrical		Absent or markedly asymmetrical	
									FACTOR SCORES	
									TOTAL SCORE	

Corrected gestational age

SCORING

Overall: Normal = 5, Mildly abnormal = 3, Markedly abnormal = 1

ITEM	0-.9	1-1.9	2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-18 months	Comments
1.	Closed		Sometimes closed	Open						Matches age = 5	One stage delay = 3 Two stage delay = 1 One closed, one open = 1
2.	0 - 15° 1			15 - 45° 2			45 - 60° 3			60 - 85° 4	5 = Picture matches age 3 = One stage away ← or → 1 = Two stages away ← or →
3.	100 - 90°			90 - 60°			60 - 40°			40 - 10°	
4.	80 - 90°			90 - 110°			110 - 150°			150 - 170°	As above except definite asymmetry = 1
5.	40 - 70°			70 - 100°			100 - 130°			130 - 150°	As for # 2 & 3
6.	0 - 10° = 1			10 - 40° = 3			40 - 70° = 5			70 - 80° = 3 80 - 90° = 1	
7.	Exaggerated Grasp = 1, Other = 5									Absent = 5 Barely Grasp = 3 Grasp = 1	
8.	Exaggerated TLS = 1, Other = 5									Absent = 5 Some = 3 Full = 1	
9.	Exaggerated ATNR = 1, Other = 5						Absent = 5			Postures in Can move out = 3 Persistent = 1	
10.							Full = 5 Partial head lag or not using arms = 3 Complete head lag and not using arms = 1				Picture matches age = 5 One stage delay = 3 Two stage delay = 1
11.					Present to both sides = 5		Slow or mildly asymmetrical = 3			Absent or markedly asymmetrical = 1	
12.										Present = 5 Poor = 3 Absent = 1	
13.	Lifts Head		Head up 45°	Forearms only	Head up 90°	Bears weight on extended forearms		All fours unsteadily	All fours well	Plantigrade	Picture matches age = 5 One stage delay = 3 Two stage delay = 1
14.	Exaggerated TLP = 1, Other = 5									Absent = 5 Some = 3 Full = 1	
15.				L3		L5					Picture matches age = 5 One stage delay = 3 Two stage delay = 1
16.							Present in both arms = 5		Slow or mildly asymmetrical = 3	Absent or markedly asymmetrical = 1	
17.										As Above	
18.	Primitive Reflex	No Weight-bearing		Poor weight bearing Breaks at knee		Unequal weight bearing					Picture matches age = 5 One stage delay = 3 Two stage delay = 1
											Persistent weight-bearing (>60 sec) at 2.5 - 5 months = 1
19.				Maintains weight feet flat = 5		5 - 30 sec. on toes then drop to feet flat = 3				> 30 sec on toes = 1	
20.								Present = 5	Slow or mildly asymmetrical = 3	Absent or markedly asym. = 1	

Degree of normality/abnormality based on total score

Less than 4 months	4 to 8 months	8 months or more
Abnormal ≤ 48	Abnormal ≤ 54	Abnormal ≤ 68
Transient 49 - 65	Transient 55-71	Transient 69-82
Normal ≥ 66	Normal ≥ 72	Normal ≥ 83

Category of abnormality

If abnormal, choose a category

☐ Spastic Tetraparesis/Dyskinesia ☐ Spastic Hemiparesis ☐ Spastic Diplegia ☐ Hypotonia

1/85

Annexure 9

Permission for using Premie Neuro Scale

Premie Neuro Manual and Score Sheet External Inbox ×

NICU Lab Pineda <pinedaniculab@gmail.com> Wed, Sep 1, 2021, 9:13 PM

to me

Hi Neha,

I am following up on an email you sent to Dr. Pineda about the Premie Neuro and further information about the scale. Attached you will find the manual and score sheet.

Best,
Erica

Premie Neuro - Scoresheet.pdf

Premie Neuro - Manual.pdf

--
Erica Gliga OTS
Research Assistant
NICU Therapy Research Laboratory
Pronouns: She/Her/Hers

USC Chan Division of Occupational Science and Occupational Therapy
University of Southern California

Annexure 10

Premie Neuro Scale

PREMIE - NEURO
A Neurological Examination for Preterm Infants

Scoring-Use Postmenstrual Age

	Item	Description	Asymmetry	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	FACTORS 1	2	3
FACTOR 1 - NEUROLOGICAL	1. ARM RECOIL	a) ≥180° b) 100-180° c) 60-100° d) <60°	R L e=level ≥ 2			b=5 a,c=3 d,e,f=1				b,c=5 a=3 d,e=1		c,d=5 b=3 a,e=1									
	2. ARM TRACTION	a) ≥180° b) 160-180° c) 120-160° d) 100-120° e) <100°	R L f=level ≥ 2			a,b=5 c=3 d,e,f=1					b=5 a,c=3 d,e,f=1				b,c=5 a,d=3 e,f=1		c,d=5 b,e=3 a,f=1				
	3. PALMAR GRASP	a) absent b) weak flexion c) medium flexion d) strong flexion spread to forearm e) very strong lifts off bed	R L f=level ≥ 2	b=5 a,c=3 d,e,f=1		b,c=5 a,d=3 e,f=1							b,c=5 d=3 a,e,f=1		c,d=5 b=3 a,e,f=1							
	4. PLANTAR GRASP	a) absent b) weak c) medium d) strong e) very strong	R L f=level ≥ 2	b=5 a,c=3 d,e,f=1		b,c=5 a,d=3 e,f=1			b,c=5 d=3 a,e,f=1						c,d=5 b=3 a,e,f=1							
	5. SCARF SIGN	a) >85° b) 60-85° c) 45-60° d) 15-45° e) 0-15°	R L f=level ≥ 2	a=5 b,c=3 d,e,f=1						b,c=5 a=3 d,e,f=1								c,d=5 b,e=3 a,f=1			
	6. POPLITEAL ANGLE	a) ≥180° b) 150-180° c) 130-150° d) 110-130° e) 90-110° f) <90°	R L g=level ≥ 2	b=5 a,c,g=3 d,e,f=1							b,c=5 a,d=3 e,f,g=1				c,d=5 b,e,f=3 a,g=1			d,e=5 c,f=3 a,b,g=1			
	7. HEEL TO EAR	a) <10° b) 10-40° c) 40-60° d) 60-90° e) 90-100° f) ≥100°	R L g=level ≥ 2	a=5 b,c,g=3 d,e,f=1			b=5 a,c=3 d,e,f,g=1					b,c=5 a,d=3 e,f,g=1							c,d=5 b,e=3 a,f,g=1			
	8. MOVEMENT TYPE	a) mostly sluggish uncoordinated, jerky or athetoid b) mostly stretching or smooth, some random, athetoid or jerky c) smooth alternating movements d) markedly asymmetrical e) mostly tremulous					a,b=5 c=3 d,e=1							b,c=5 a=3 d,e=1								
FACTOR 2 - MOVEMENT	9. TREMORS	MINUTES ____ ____ NO. ____ RATE/MINUTE ____.____ ____				0-1.50=5 1.51-1.80=3 1.81 up=1			0-.90=5 .91-1.10=3 1.11 up=1			0-.80=5 .81-1.00=3 1.01 up=1				0-.70=5 .71-.90=3 .91 up=1					
	10. THRASHING	____ ____.____ ____				0-1.50=5 1.51-1.80=3 1.81 up=1			0-.75=5 .76-.95=3 .96 up=1			0-.50=5 .51-.60=3 .61 up=1									
	11. FACIAL GRIMACE	____ ____.____ ____		0-.20=5 .21-.30=3 .31 up=1		0-.30=5 .31-.50=3 .51 up=1			0-.40=5 .41-.60=3 .61 up=1			0-.50=5 .51-.70=3 .71 up=1	0-.60=5 .61-.80=3 .81 up=1								
	12. STARTLE	____ ____.____ ____		0-.40=5 .41-.60=3 .61 up=1	0-.50=5 .51-.70=3 .71 up=1		0-.60=5 .61-.80=3 .81 up=1					0-.50=5 .51-.70=3 .71 up=1				0-.40=5 .41-.60=3 .61 up=1					
	13. YAWN	____ ____.____ ____					0-.40=5 .41-.60=3 .61 up=1						0-.50=5 .51-.70=3 .71 up=1		0-.60=5 .61-.80=3 .81 up=1		0-.50=5 .51-.70=3 .71 up=1				
	14. COLOR CHANGE	____ ____.____ ____			0-.50=5 .51-.70=3 .71 up=1			0-.40=5 .41-.60=3 .61 up=1			0-.30=5 .31-.50=3 .51 up=1					0-.20=5 .21-.30=3 .31 up=1					
	15. ARM MOVEMENTS	____ ____.____ ____				0-0.8=5 .9-1.3=3 1.4 up=1				0-0.9=5 1.0-1.4=3 1.5 up=1		0-1.0=5 1.1-1.5=3 1.6 up=1	0-1.2=5 1.3-1.7=3 1.8 up=1	0-1.5=5 1.6-2.0=3 2.1 up=1	0-1.2=5 1.3-1.7=3 1.8 up=1		0-1.0=5 1.1-1.5=3 1.6 up=1				
	16. LEG MOVEMENTS	____ ____.____ ____						0-0.9=5 1.0-1.4=3 1.5 up=1				0-1.0=5 1.1-1.5=3 1.6 up=1			0-0.9=5 1.0-1.4=3 1.5 up=1		0-0.8=5 .9-1.3=3 1.4 up=1				
FACTOR 3 - RESPONSIVENESS	17. ARM FLEXION	a) >170° b) 140-170° c) 110-140° d) 70-110° e) <70°	R L f=level ≥ 2						a,b=5 c,f=3 d,e=1		b=5 a,c=3 d,e,f=1							b,c=5 a,d=3 e,f=1			
	18. HEAD LAG	a) b) c) d) e)								a,b=5 c=3 d,e=1				b,c=5 a,d=3 e=1				c,d=5 b,e=3 a=1			
	19. HELD SIT	a) head stays forward or backward b) head up <3 seconds c) head up 3-10 seconds d) head up >10 seconds							a=5 b=3 c,d=1			a,b=5 c=3 d=1			b,c=5 d=3 a=1						
	20. POSTERIOR NECK	a) no attempt to raise head b) tries but cannot raise head c) head upright by 30 seconds, drops head d) head upright by 30 seconds, maintained e) examiner cannot extend head								a,b=5 c=3 d,e=1			b,c=5 a,d=3 e=1				c,d=5 b=3 a,e=1			
	21. ANTERIOR NECK	a) no attempt to raise head b) tries but cannot raise head c) head upright by 30 seconds, drops head d) head upright by 30 seconds, maintained e) examiner cannot flex head								a,b=5 c=3 d,e=1					b,c=5 a,d=3 e=1		c,d=5 b=3 a,e=1				
	22. ALERT	a) 0-4 sec b) 5-10 sec c) 11-30 sec d) 31-60 sec e) >60 sec							a=5 b=3 c,d,e=1	a,b=5 c=3 d,e=1			b,c=5 a,d=3 e=1				c,d,e=5 b=3 a=1			
	23. VENTRAL SUSPENSION	a) b) c) d) e)									a,b=5 c=3 d,e=1		b,c=5 a,d=3 e=1				c,d=5 b,e=3 a=1			
	24. RESPONSIVENESS	a) not very responsive b) average c) very responsive										b,c=5 a=3			c=5 b=3 a=1						

©Daily and Ellison
(09/02) REV. 12/04

Hosp. No. _____ Sex: ☐ F ☐ M _____
Name _____ Gestational age at birth _____
Date of birth _____ Postmenstrual age at exam _____
Date of exam _____ Birth weight _____

<28 weeks/on respirator
Abnormal = <50
Questionable = 50-69
Normal = 70-80

≥28 weeks/off respirator
Abnormal = <70
Questionable = 70-99
Normal = ≥100

Subtotals
Total